IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

UNITED THERAPEUTICS CORPORATION, Plaintiff, v. LIQUIDIA TECHNOLOGIES, INC., Defendant.	)	**Redacted - Public Version** C.A. No. 23-975-RGA-SRF [redacted]

DEFENDANT LIQUIDIA TECHNOLOGIES, INC.'S ANSWERING BRIEF IN OPPOSITION TO UTC'S MOTION FOR LEAVE TO FILE A MOTION FOR SUMMARY JUDGMENT REGARDING LIQUIDIA'S INEQUITABLE CONDUCT COUNTERCLAIM

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I. SUMMARY OF ARGUMENT

In this Hatch-Waxman case, UTC moves for leave to immediately file a motion for summary judgment ("MSJ") regarding Liquidia's inequitable conduct counterclaim. However, UTC's motion lacks good cause to warrant filing summary judgment prior to the close of expert discovery. As the Scheduling Order makes clear, and consistent with the practice in this Court, dispositive motions in a Hatch-Waxman case are not permitted without leave from the Court. *See* D.I. 45 at ¶10.

Liquidia and UTC both believe that certain issues in this case may be amenable for resolution by summary judgment and as discussed below, Liquidia offered a reasonable compromise that allows both parties to seek early resolution of specific issues. Instead, UTC proposes a piecemeal briefing process during the midst of expert discovery, while at the same time (1) reserving its right to file an expert declaration in support of its motion, (2) reserving its right to serve an expert report in the normal course of expert discovery addressing inequitable conduct, and (3) reserving its nonexistent right to file additional requests for leave to file summary judgment ***at a later*** time. This approach directly undermines judicial efficiency and contradicts principles this Court has applied in similar cases. Here, UTC's proposal—filing a summary judgment motion on an issue that is heavily factual in nature while reserving on further motions for summary judgment—would exacerbate inefficiencies and burden both the parties and the Court.

Liquidia, however, believes that motion practice could serve to substantially narrow the issues for trial in an efficient manner, but only following a schedule normally adopted by the Court in non-ANDA cases—after the close of expert discovery—a compromise that preserves both the parties and Court's time and resources. To this end and in an attempt to avoid unnecessary motion practice, Liquidia made this offer to UTC during the parties' January 9, 2025 meet and confer.

(*See* Ex. 1 (1/9/2025 Email by J. Habibi) at 2-3.) Counsel for UTC rejected Liquidia's proposal out of hand and instead decided to burden the Court with this motion when it could have been easily resolved without intervention. Even after UTC filed its motion, Liquidia made another attempt to resolve this issue amicably, which UTC similarly declined. (Ex. 2 (1/13/2025 Email by S. Sukduang) at 1-2.)

Finally, while UTC improperly engages in a merit-based argument in its motion for leave, it overlooks material facts in dispute that preclude summary judgment. Liquidia's inequitable conduct counterclaim is supported by the facts, including testimony and documents showing that during the prosecution of U.S. Patent No. 11,826,327 (the "'327 patent"), UTC's in-house and outside counsel intentionally withheld material information, including information from this Court and submissions made to the Patent Trial and Appeal Board ("PTAB"), confirming the subject matter of the '327 patent claims were already patented and claimed by UTC. This information is "but for" material to the patentability of the '327 patent, both UTC's in-house and outside counsel were aware of this information, and the most reasonable inference to be drawn, in the light most favorable to Liquidia at the summary judgment stage, is that they intentionally withheld it from the PTO Examiner in order to obtain another Orange Book listable patent it can use to protect its multi-billion-dollar treprostinil franchise.

For these reasons, Liquidia respectfully requests that the Court deny UTC's motion for leave to file summary judgment prior to the close of expert discovery. To the extent the Court is inclined to entertain MSJs, Liquidia respectfully requests that briefing be scheduled after the close of expert discovery to preserve judicial economy, as Liquidia proposed on the parties January 9 meet and confer.

II. NATURE & STAGE OF PROCEEDINGS AND STATEMENT OF FACTS

A. UTC's Assertion of the '793 and '327 Patents

This case concerns Liquidia's amended NDA adding the PH-ILD indication for its Yutrepia™ product. Based on that amendment, UTC initially filed suit against Liquidia on September 5, 2023, asserting U.S. Patent No. 10,716,793 (the "'793 patent"). *See* D.I. 1. UTC asserted the '793 patent on September 5, 2023, despite the fact that earlier, on July 19, 2022, the PTAB issued its Final Written Decision invalidating the claims of the '793 patent. *See* D.I. 12 at ¶73; *id.* at Ex. 31 (PTAB Final Written Decision). Importantly, Mr. Shaun Snader and Mr. Stephen Maebius (UTC's in-house and outside counsel, respectively) knew the '793 patent was found to be invalid during prosecution of the application leading to the '327 patent, which did not issue until November 28, 2023. On November 30, 2023, UTC amended its complaint to assert the '327 patent. *See* D.I. 8. Liquidia filed its Answer and Counterclaims on January 8, 2024, wherein Liquidia's counterclaims asserted that Mr. Snader and Mr. Maebius engaged in inequitable conduct during prosecution of the '327 patent by withholding material information from the '793 patent *Inter Partes* Review ("IPR") as well as information from this Court concerning the scope of the '793 patent claims. *See* D.I. 12 at ¶¶36, 66-92, 104-117. UTC did not move to dismiss Liquidia's inequitable conduct counterclaim. Because the Federal Circuit affirmed the PTAB's Final Written Decision invalidating the '793 patent, UTC dismissed its '793 patent infringement allegations on January 22, 2024, leaving only the '327 patent in suit. *See* D.I. 17.

B. A Synopsis of Mr. Snader's and Mr. Maebius' Inequitable Conduct During Prosecution of the '327 Patent

Mr. Snader and Mr. Maebius were both involved in the prosecution of the application leading to the '327 patent and had a duty of disclosure. (*See* Ex. 3 (Maebius Dep. Tr.) at 24:10-19, 43:17-21; Ex. 4 (Snader Dep. Tr.) at 40:2-44:2.) Both Mr. Maebius and Mr. Snader were

deposed during the course of discovery in this case, and while they refused to answer the vast majority of questions posed to them on the basis of attorney-client privilege, the testimony they did provide offered key admissions supporting the materiality and intent elements of their inequitable conduct.

Mr. Maebius testified that [redacted]; that he was counsel of record for UTC in the '793 patent IPR and aware of UTC's statements concerning the fact that the '793 patent claims were directed to treating PH-ILD, including improving exercise capacity; and that particular information was not submitted to the PTO during prosecution of the '327 patent. (*See* Ex. 3 at 24:17-19; 84:2-11, 87:2-13, 145:12-146:1.) Similarly, Mr. Snader confirmed that he was counsel for UTC in the '793 patent's IPR proceedings, [redacted]; was present during the trial before this Court concerning the '793 patent; [redacted] *See* Ex. 4 at 102:21-103:4, 104:2-14, 104:22-105:15, 106:5-107:18, 140:13-141:10, 150:16-151:13, 229:19-237:2; Ex. 5 at LIQ_PH-ILD_00000852.

C. Liquidia's Attempts to Streamline Resolution

On the afternoon of January 6, 2025, UTC's counsel emailed Liquidia's counsel to announce, for the first time, its intent to file a motion seeking leave to file summary judgment regarding Liquidia's inequitable conduct counterclaim. (Ex. 1 at 8.) In that email, UTC demanded that Liquidia either consent, oppose, or meet and confer on the same day. (*Id.*) In response,

Liquidia's counsel indicated availability for January 9, 2025, to allow for meaningful preparation and discussion. (*Id.* at 3-4.)

During the January 9, 2025 meet and confer, UTC informed Liquidia that if its motion for leave were granted, it would ***immediately*** file its MSJ, despite the fact that expert discovery is ongoing. UTC further indicated that even if granted leave to file its MSJ now, it reserved the right to (1) submit an expert declaration in support of its MSJ, (2) submit an expert report responsive to Liquidia's expert addressing UTC's inequitable conduct, and (3) file additional requests for leave to file MSJs at a later, undefined time. (*Id.* at 2-3.) Liquidia pointed out that UTC's approach would increase burden on the parties, force the Court to address requests for leave and act on MSJs in a piecemeal fashion, and negate any efficiencies typically achieved through summary judgment. UTC did not explain during the meet and confer or in its submission how its approach could possibly save time or resources for the parties or the Court, nor could it explain any prejudice to UTC in having to wait, other than wanting the claim out of the case now.

In the spirit of compromise, Liquidia proposed a reasonable, efficient alternative consistent with standard MSJ practice in this Court. Specifically, Liquidia offered the following:

1. Subject to Court approval, both parties would be permitted to file one MSJ;
2. MSJs would be filed only after the close of expert discovery; and
3. To the extent the Court seeks oral arguments on MSJs, such oral arguments would occur at the pre-trial conference or on a mutually agreed-upon date. Counsel for Liquidia also expressed willingness to consider a counter-proposal regarding the date for oral argument.

(*Id.*) This proposal considers the time required for briefing, ensures that a full evidentiary record would be available for the Court to consider, prevents the Court from having to address MSJs in a piecemeal fashion, and, importantly, eliminates the motion practice UTC has now engaged in.

Despite this proposal, UTC immediately refused Liquidia's offer on the sole basis that there was no "factual" basis for Liquidia's inequitable conduct allegations. Recognizing the detrimental nature of its hasty refusal, counsel for UTC later claimed that "in advance of the call, [it] discussed

and confirmed with the client that the types of conditions that Liquidia ultimately identified would be unacceptable." (*Id.* at 1-2.) However, this assertion is both unverifiable and implausible, as Liquidia's specific proposal was presented during the meet and confer. After reviewing the Court's briefing schedule with respect to UTC's pending motion, Liquidia once again offered to compromise and provide the Court with a unified summary judgment schedule. (*See* Ex. 2 at 2.) UTC refused. (*See id*. at 1-2.)

III. ARGUMENT

A. UTC Has Not Demonstrated Good Cause to File a Motion for Summary Judgment at This Stage

UTC's motion for leave fails because it does not establish the required good cause to deviate from the Scheduling Order and file summary judgment prior to the close of expert discovery. The Scheduling Order expressly provides that "[n]o case dispositive motions shall be filed without leave of Court." *See* D.I. 45 at ¶10. By seeking leave to file summary judgment now, UTC is requesting a modification of the Scheduling Order. Under Rule 16(b)(4), such a modification requires a showing of good cause. *See* FED. R. CIV. P. 16(b)(4); *ICU Med., Inc. v. RyMed Techs., Inc.*, 674 F. Supp. 2d 574, 577 (D. Del. 2009) (internal quotation marks omitted) (citation omitted). UTC's motion fails to meet this standard and fails to provide any valid reason why filing summary judgment before the close of expert discovery is necessary.

1. Filing Summary Judgment Before the Close of Expert Discovery is Unwarranted

UTC's proposal to file its MSJ prior to the close of discovery is inconsistent with procedural norms of Hatch-Waxman cases in Delaware, and this case specifically, where MSJs generally are not permitted. *See* D.I. 45 at ¶10. While Liquidia agrees that filing MSJs could help narrow the issues for trial in an efficient manner, the efficiency of MSJ practice in this case would

be undermined if the MSJs are filed before expert discovery is complete and before the full evidentiary record has been completed.

Under the current schedule, opening expert reports were served on December 20, 2024; responsive expert reports are due on January 23, 2025; reply expert reports are due on February 14, 2025; and expert depositions must be completed by March 7, 2025. As discussed during the meet and confer, under the most expeditious schedule, the opening MSJ briefs would be submitted before expert discovery is complete, depriving the parties and the Court of a complete evidentiary record. UTC's proposed motion is thus too premature to allow the Court a complete record, and too late to save the parties and the Court from expert discovery and unnecessary motion practice. It is inefficient and it disrupts the orderly progression of discovery and motion practice. Indeed, in the prior litigation between the parties, UTC opposed Liquidia's motion for leave to file summary judgment arguing that because expert discovery is ongoing, "it would be inefficient to engage in summary judgment motion practice prior to the close of expert discovery." *See* Ex. 6 (*United Therapeutics Corp. v. Liquidia Techs., Inc.*, No. 20-cv-755, D.I. 253 at *7 (D. Del. Nov. 23, 2021)).

This Court has repeatedly emphasized that MSJs filed before the close of discovery are inappropriate, as they undermine the Court's ability to evaluate the issue based on a fully developed factual record. *See Sprint Commc'ns Co. v. Charter Commc'ns, Inc.*, No. 17-cv-1734, 2021 WL 982728, at *4 (D. Del. Mar. 16, 2021); Ex. 7 (*Fundamental Innovation Sys. Int'l LLC v. Lenovo (United States), Inc.*, No. 20-cv-551, D.I. 68 (D. Del. Nov. 23, 2021)); Ex. 8 (*United Therapeutics Corp. v. Liquidia Techs., Inc.*, No. 20-cv-755, D.I. 267 (D. Del. Dec. 14, 2021)) (granting leave to move for summary judgment of invalidity as to a legal issue (collateral estoppel) but denying request for leave to file MSJ of invalidity as to a factual issue (obviousness) before

the close of expert discovery). UTC's approach violates this principle, as its motion would proceed without the benefit of expert analysis that is critical to resolving the factual disputes underlying Liquidia's inequitable conduct counterclaim.

The sole justification for its request to file summary judgment now is a passing reference to the possibility of a jury trial in this case. *See* D.I. 239 at 1. UTC's argument is without merit. UTC did not demand a jury trial in its complaint or at any point during this litigation. *See* D.I. 1; D.I. 8; *see also* FED. R. CIV. P. 38(b), (d) (providing that the right to a trial by jury is waived if not demanded within 14 days after last pleading is served). Even if it had, following the process proposed by Liquidia would allow the MSJs to be resolved in advance of trial. Moreover, because UTC has not submitted an expert report on damages, it is foreclosed from submitting a damages expert report in this case, further undermining its claim to a trial by jury. Finally, to the extent UTC seeks damages, it must file a new case, especially because the deadline to amend the pleading (April 4, 2024) has passed. *See Astellas Pharma Inc. v. Sandoz Inc.*, No. 20-cv-1589, 2024 WL 4554799, at *1-2 (D. Del. Oct. 22, 2024 (holding that Hatch-Waxman cases generally provide only equitable remedies and that damages claims require a separate action); D.I. 45 at ¶ 2. Thus, UTC's mention of a jury trial is not a basis to file summary judgment prior to the close of expert discovery.

2. UTC's Request Undermines Judicial Efficiency

UTC's proposal to file a MSJ during ongoing expert discovery while reserving the right to file additional MSJs at a later date undermines the very purpose of summary judgment—to streamline litigation and promote judicial economy. *See Friction Div. Prods., Inc. v. E.I. Du Pont de Nemours & Co.*, 693 F. Supp. 114, 120 (D. Del. 1988). As it stands, UTC reserved the right to (1) file an expert declaration in support of its MSJ, (2) serve an expert report in the normal course

of expert discovery addressing inequitable conduct,[1] and (3) file additional MSJs after the close of discovery. This fragmented approach would impose significant and unnecessary burdens on the Court, forcing it to evaluate MSJ issues at multiple stages of the case. UTC has failed to demonstrate how its proposed MSJ would save time or resources for the parties or the Court.

Liquidia's proposed compromise ensures that MSJs are addressed at the appropriate time and in a manner that minimizes unnecessary piecemeal decisions and has the benefit of a complete record. As discussed above, Liquidia suggested that (1) both parties be permitted to file a single MSJ, (2) MSJs be filed after the close of expert discovery, and (3) oral argument on summary judgment, if requested, be held at the pre-trial conference or a mutually agreed-upon date. (*See* Ex. 1 at 2-3.)

Furthermore, UTC's suggestion that early summary judgment briefing would "conserve resources and avoid the need for a separate bench trial on inequitable conduct" is contradicted by the very nature of the present Hatch-Waxman case, which is a bench trial. *See* Ex. 9 (*Leo Pharma A/S v. Perrigo UK Finco Ltd. P'ship*, No. 16-cv-430, D.I. 394 at *3-4 (D. Del. Sept. 13, 2018)) (denying leave to file summary judgment close to trial because inequitable conduct claims were better suited for resolution during a bench trial, ensuring a full evidentiary record). These claims involve highly factual determinations, such as intent, that require a full evidentiary record and credibility determinations to resolve. UTC's piecemeal approach would create confusion, delay resolution, and increase costs for the parties.

[1] Liquidia's opposition to UTC's motion for leave is also due on January 23, 2025, the same day responsive expert reports are due. Thus, as of the date of this submission, Liquidia does not yet know if UTC will submit a responsive expert report on the issue of inequitable conduct. Liquidia will promptly inform the Court if UTC does serve a responsive expert report on the issue of inequitable conduct.

In sum, Liquidia is willing to engage in MSJ briefing after the close of expert discovery and believes it may help resolve certain issues before trial. UTC's schedule is simply inefficient and premature, whereas Liquidia's proposal on MSJ timing promotes efficiency and permits summary judgment on a complete record. Accordingly, to the extent the Court is inclined to hear summary judgment, Liquidia respectfully requests the Court adopt Liquidia's proposed schedule.

B. Genuine Disputes of Material Fact Regarding UTC's Inequitable Conduct Preclude Summary Judgment

UTC's motion spends no time addressing why it should be permitted to file summary judgment before expert discovery is complete and instead argues the merits of its proposed motion on inequitable conduct and why it will prevail. That's not the purpose of this motion. Nonetheless, UTC's preview of its summary judgment motion distorts the factual record.

Courts grant summary judgment if the moving party shows that there is no genuine dispute as to any material fact and that the moving party is entitled to judgment as a matter of law. FED. R. CIV. P. 56(a). Initially, the moving party has the burden of proving the absence of a genuinely disputed material fact. *See Celotex Corp. v. Catrett*, 477 U.S. 317, 330 (1986).

The burden shifts to the non-moving party to demonstrate that a genuine issue of material fact does exist. *Matsushita Elec. Indus. Co. v. Zenith Radio Corp.*, 475 U.S. 574, 586-87 (1986). During summary judgment, when determining whether a genuine issue of material fact exists, the court must view the evidence in the light most favorable to the non-moving party (Liquidia) and draft all reasonable inferences in that party's favor. *Scott v. Harris*, 550 U.S. 372, 380 (2007).

In the context of inequitable conduct, determining materiality and intent requires careful consideration of the factual record, and disputes regarding these issues are typically unsuitable for summary judgment. *See Sprint Commc'ns*, 2021 WL 982728, at *4. Here, genuine disputes of material fact exist as to both the materiality of the withheld information and UTC's intent to

deceive the PTO. *See Scott*, 550 U.S. at 380. Indeed, the evidence demonstrates that UTC failed to disclose multiple references that are but-for material to the issuance of the '327 patent.

1. Genuine Disputes of Material Fact Regarding Materiality

Liquidia's inequitable conduct counterclaim is based on UTC's failure to disclose "but-for" material information to the PTO regarding the '793 patent. *See* D.I. 12 at ¶¶36, 66-92, 104-117. Specifically, UTC failed to disclose this Court's claim construction opinion addressing the scope of the '793 patent claims, Dr. Hill's trial testimony regarding the '793 patent, the Federal Circuit's affirmance of the Court's claim construction opinion, and submissions from the '793 IPR, including the Patent Owner Response, a declaration by Dr. Aaron Waxman, and the Final Written Decision (collectively the "Asserted References"). It is undisputed that the Asserted References were not disclosed to the PTO. UTC argues that these references are cumulative of the '739 patent and, therefore, not material. This argument fails for several reasons.

UTC argues that summary judgment is warranted because "[t]he evidence adduced in the District Court Litigation" and the "'793 IPR" submissions are "cumulative of the '793 patent and cannot serve as the basis for an inequitable conduct claim[,]" that the "'793 patent's plain and ordinary meaning of 'pulmonary hypertension'" encompasses "all five WHO groups, including interstitial lung disease[,]" that "[n]othing in the record suggests that the Examiner applied a different definition" than the one presented during the District Court litigation and the '793 IPR, and finally that the Asserted References are cumulative of four references disclosed to the PTO—Agarwal 2015, WO 2008/098196 A1 ("Wade"), WO 2016/205202 A1 ("Zhang")[2], and WO 2015/138423 A1 ("Malinin") because they teach the "exact information Liquidia alleges was

[2] UTC referred to the reference as "Wang" in its response to the Examiner's rejection, but this appears to be a typographical error. The correct reference, as identified elsewhere in the record, is "Zhang."

withheld."[3] *See* D.I. 239 at 3-5. However, a "reference is cumulative when it *teaches no more* than what a reasonable examiner would consider to be taught by the prior art *already before* the PTO." *Luv N' Care, Ltd. v. Laurain,* 98 F.4th 1081, 1098 (Fed. Cir. 2024) (holding that while the prior art itself was disclosed to the PTO, misrepresentations or omissions about what the prior art disclosed, such as the scope of teachings of the references, could demonstrate an intent to deceive); *see also Graphics Props. Holdings, Inc. v. Google Inc.*, Nos. 12-cv-1394, -1397, 2014 WL 6629021, at *2 (D. Del. Nov. 20, 2014) (dismissing the argument that the patentee had no need to disclose further litigation after disclosing the underlying appealed district court order because the Federal Circuit opinion contained relevant statements not in the district court opinion). The Federal Circuit has also held that information from prior patent litigation proceedings is material. *See Leviton Mfg. Co. v. Universal Sec. Instruments, Inc.*, 606 F.3d 1353, 1362 (Fed. Cir. 2010) (finding patentee's failure to disclose existence of earlier related litigation was "material" to its application for patent despite patentee's claim that it was not material due to its success on the validity of the patents in earlier litigation); *Nilssen v. Osram Sylvania, Inc.*, 504 F.3d 1223, 1233-34 (Fed. Cir. 2007) (holding that the existence of earlier related litigation itself was material information).

Here, the Asserted References provide details about the scope of the '793 patent that the Examiner would not have known based on the materials UTC asserts were sufficient, namely: the '793 patent itself, the '793 IPR petition, and the four references (Agarwal 2015, Wade, Zhang, and Malinin). As explained herein, the withheld Asserted References include statements and evidence demonstrating how the '793 patent claims include treating PH-ILD patients and improving

[3] The Examiner never relied on the '793 patent to reject the '327 patent claims, and thus there is no basis for UTC's assertion that the Examiner applied ***any*** definition of "pulmonary hypertension."

exercise capacity—information that would be critical to the Examiner's evaluation of the '327 patent claims to the same subject matter. [redacted] (*See* Ex. 3 at 87:2-13.)

During the '793 IPR, UTC argued in its Patent Owner Response that the claims of the '793 patent satisfies a long-felt unmet need in the treatment of PH stating that "[i]nhaled treprostinil is currently approved for pulmonary arterial hypertension ***and pulmonary hypertension associated with interstitial lung disease***." (*See* Ex. 10 (Patent Owner Response) at LIQ_PH-ILD_00000180 (emphasis added).) Dr. Aaron Waxman's declaration supporting UTC's argument that the '793 patent claims satisfy a long-felt unmet need reinforced this position, stating that "[i]nhaled treprostinil is also approved to treat a broader range of [PH] patients than the therapeutics available at the time of the invention" and that "[a]t the time of the claimed invention, even as of today, there are no other therapies approved for the treatment of [PH] in patients with [ILD]." (*See* Ex. 11 (Waxman IPR Decl.) at LIQ_PH-ILD_102081, ¶¶95-96.) Mr. Snader and Mr. Maebius, as IPR counsel for UTC, were aware of and affirmatively submitted these statements to the PTAB.

Messrs. Maebius and Snader testified that the Patent Owner Response statements regarding long-felt unmet need referred to the claims of the '793 patent. (*See* Ex. 3 at 136:1-7; Ex. 4 at 137:12-22, 138:19-139:24.) Mr. Maebius also testified that this statement indicates that the '793 patent ***claims*** the approved PH-ILD indication on the Tyvaso® label, which reads: "Tyvaso is indicated for the treatment of pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3) to improve exercise ability."[4] (*See* Ex. 3 at 137:3-13; Ex. 12 (Tyvaso®

[4] This is also self-evident by UTC's litigation actions as it asserted the '793 patent against Liquidia when Liquidia amended its NDA to add the PH-ILD indication: "YUTREPIA is indicated for the treatment of pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO

Label) at UTC_PH-ILD_010745.) In other words, Messrs. Maebius and Snader told the PTAB that the '793 patent claims the same subject matter as the '327 patent. This is material information that was not before the PTO during prosecution of the '327 patent.

Similarly, the Court construed "pulmonary hypertension" in the '793 patent claims to include "all five Groups of PH." *United Therapeutics Corp. v. Liquidia Techs., Inc.*, 624 F. Supp. 3d 436, 464-66 (D. Del. 2022), *aff'd*, 74 F.4th 1360 (Fed. Cir. 2023). This means that under the Court's construction, the '793 patent claims include treating PH-ILD patients, the same patient population as the '327 patent. This information was not before the Examiner.

UTC's current argument that the Asserted References are cumulative to the '793 patent, and the '793 patent's "plain and ordinary meaning" of pulmonary hypertension includes PH-ILD and improving exercise capacity in PH-ILD patients, run counter to UTC's other arguments made ***in this case*** regarding the '793 patent. For example, in support of its motion for a preliminary injunction, Dr. Nathan, UTC's expert, stated that "[a] POSA would not understand the '793 patent to teach the administration of treprostinil to improve exercise capacity in a patient having PH-ILD[.]" *See* D.I. 28 (Nathan PI Decl.) at ¶176. During the preliminary injunction oral argument, UTC's counsel argued to the Court that (1) the '793 patent teaches the treatment of a "different patient class" than the '327 patent; and (2) "there is nothing in the '793 patent whatsoever about exercise capacity, period, full stop. The words just don't even appear in there." (*See* Ex. 13 (PI Hearing Tr.) at 24:2-25; 66:5-8; *see also id.* at 25:7-26:12, 68:22-69:6.) And in its response to Liquidia's Interrogatory No. 1, UTC asserted that the "'793 patent claims do not express specific preferences for treating PH-ILD." (*See* Ex. 14 (UTC Am. First Suppl. Resp. to Interrog. No. 1) at

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Group 3) to improve exercise ability." *See* D.I. 1; Ex. 15 (Proposed Yutrepia™ Label) at LIQ_PH-ILD_00126021.

26.) To the extent UTC wished to stipulate that the '793 patent covers improving exercise capacity in PH-ILD patients as set forth in the Asserted References, Liquidia could then agree that this fact is not in dispute. Because UTC continues to argue the '793 patent is not directed to treating PH-ILD or improving exercise capacity in PH-ILD patients, it cannot simultaneously contend that the Asserted References are cumulative to the '793 patent. At a minimum, given UTC's often inconsistent arguments as to the scope of the '793 patent, genuine issues of material fact exist as to materiality, precluding summary judgment.

Furthermore, the Asserted References are not cumulative to the four references cited in UTC's motion. *See* D.I. 239 at 3-4. Firstly, none of the four references provide the same detailed insights into the scope of the '793 patent as the Asserted References. Next, none of the references teach the information in the Asserted References relating to the '793 patent, such as improving exercise capacity in PH-ILD patients with inhaled treprostinil or specific dosing regimens. In fact, to overcome the Examiner's rejection, UTC amended the claims and argued that both Malinin and Zhang do "not teach or suggest" elements of claim 1; "teach[] nothing regarding either treprostinil doses for inhalation or an amount of treprostinil administered per breadth[;]" and also that Zhang "teaches nothing regarding improving exercise capacity in any patient." (Ex. 16 at UTC_PH-ILD_009742-443.) But the Asserted References establish the '793 patent teaches all of this.

Additionally, UTC's conduct during the prosecution of other patent applications similar to the '327 patent further supports the materiality of the Asserted References. During prosecution of U.S. Patent No. 11,723,887 (also listed in the Orange Book for Tyvaso®), Mr. Maebius submitted documents from district court proceedings (including invalidity contentions) as well as IPR proceedings (including Petitions, Demonstratives, Patent Owner's Responses, Petitioner's Reply to Patent Owner Responses, and Final Written Decisions). (*See* Ex. 17 at LIQ_PH-

ILD_00101325-328.) This evidences his understanding that information from district court litigations are to be submitted during prosecution of applications on similar subject matter, which he failed to do here. Additionally, as Dr. Hill explains, Mr. Maebius filed "Notifications of Related Proceedings" in other patent applications disclosing '793 IPR documents including the '793 IPR Institution Decision, Patent Owner's Preliminary Response to Petition, Petitioner's Reply, Patent Owner's Sur-Reply, and the Final Written Decision. (*See* Ex. 18 (Hill Report) at ¶¶266-268, n.280.) The fact that Mr. Maebius[5] filed these documents in other applications while prosecution of the '327 patent was ongoing, but withheld them from the examiner during prosecution of the '327 patent itself, underscores their materiality.[6]

Viewed in the light most favorable to Liquidia, these Asserted References are but-for material to the patentability of the '327 patent as they contain UTC's admissions that the '793 patent covers improving exercise capacity in PH-ILD patients—the exact subject matter of the '327 patent. UTC's selective characterization and recharacterization of the '793 patent in this very case underscores UTC's efforts to shape its summary judgment arguments to support its assertion that Mr. Snader and Mr. Maebius did not commit inequitable conduct. At the very least, the conflicting evidence and UTC's own contradictions create a genuine dispute of material fact regarding materiality, precluding summary judgment.

2. Genuine Disputes of Material Fact Exist Regarding Intent

UTC's in-house and outside counsel, Mr. Snader and Mr. Maebius, respectively, intentionally withheld the Asserted References from the PTO during prosecution of the '327 patent

[5] [redacted] (*See* Ex. 3 at 43:17-46:17.)

[6] It also allows for the reasonable inference that Mr. Maebius intentionally withheld these references from the PTO during prosecution of the '327 patent.

in order to obtain its allowance. UTC argues that Liquidia has failed to provide sufficient evidence of specific intent to deceive the PTO because "the Examiner's attention was specifically drawn to the '793 patent, which the '327 patent 'incorporated' 'in its entirety.'" D.I. 239 at 5 (quoting '327 patent). As discussed herein, the '793 patent was "incorporated" by reference into the '327 patent for its disclosure of a "pulsed inhalation device[]," and does not evidence a lack of intent because Mr. Snader and Mr. Maebius still intentionally withheld their own statements regarding what the claims of the '793 patent actually cover—the same subject matter as the '327 patent claims.

Intent to deceive the PTO is a factual determination that may be inferred from circumstantial evidence. *See Therasense, Inc v. Becton, Dickinson & Co.*, 649 F.3d 1276, 1290 (Fed. Cir. 2011); *Digit. Control, Inc. v. Charles Mach. Works,* 437 F.3d 1309, 1317 (Fed. Cir. 2006) ("Direct evidence of intent is rare, such that a court must often infer intent from the surrounding circumstances"); *Sprint Commc'ns*, 2021 WL 982728, at *4. At the summary judgment stage, summary judgment of no inequitable conduct should be denied if, "drawing all reasonable inferences in favor of [the nonmoving party], a reasonable factfinder *could reasonably find* that intent to deceive is the single most reasonable inference." *See Sysmex Corp. v. Beckman Coulter, Inc.*, No. 19-cv-1642, 2022 WL 1503987, at *4 (D. Del. May 6, 2022) (citing *Sprint*, 2021 WL 982728, at *4-5). Particularly pertinent here is the fact that "purposeful omission or misrepresentation of key teachings of prior art references may, instead, be indicative of a specific intent to deceive the PTO." *Luv N' Care,* 98 F.4th at 1099.

Here, Liquidia has presented sufficient evidence from which a factfinder could reasonably conclude that Mr. Snader and Mr. Maebius acted with intent to deceive the PTO. By way of

example, the following evidence demonstrates Mr. Snader's and Mr. Maebius' intent to deceive by selectively withholding key teachings of the '793 patent:[7]

(1) During prosecution of the '327 patent, Messrs. Maebius and Snader were aware that the PTAB had rendered all '793 patent claims unpatentable because they were IPR counsel, and that UTC had no other Orange Book listed patents it could assert against Liquidia to protect UTC's multi-billion-dollar treprostinil franchise. (*See* Ex. 18 at ¶¶250-251.)

(2) Messrs. Maebius and Mr. Snader were actively involved in UTC's submissions to the PTAB during the '793 IPR, the District Court litigation, and their respective hearings, where numerous statements were made asserting that the '793 patent claims encompassed PH-ILD and improving exercise capacity in such patients. (*See e.g.*, *id.* at ¶¶242-265.)

(3) If Messrs. Maebius and Snader believed that the '793 IPR filings were cumulative of the '793 patent itself, as UTC now asserts, then they would not have submitted the '793 IPR petition during prosecution of the '327 patent, while withholding other '793 IPR filings, including UTC's Patent Owner Response, Dr. Waxman's Declaration, and the Final Written Decision. Their selective disclosure is sufficient evidence of their intent to deceive.

(4) While prosecution of the '327 patent was pending, Messrs. Maebius and Snader disclosed '793 IPR filings—including the '793 IPR Institution Decision, Patent Owner's Preliminary Response to Petition, Petitioner's Reply, Patent Owner's Sur-Reply, and the Final Written Decision—through "Notifications of Related Proceedings" in other patent applications that are in the same family as the '793 patent and cover similar subject matter as the '327 patent.[8]

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[7] [redacted] (*See* Ex. 18 at ¶¶213-268.)

[8] *See supra* Section III.B.1.

However, they deliberately withheld these same '793 IPR filings from the PTO in connection with the then-pending '327 patent application. Again, their selective disclosure is sufficient evidence of their intent to deceive.

(5) On February 12, 2024, UTC sent a letter to the FDA stating, "UTC received approval of the new PH-ILD indication" and referred to the "litigation on the ***patents covering the new indication—the '793 patent***, and U.S. Patent No. 11,826,327[.]" (Ex. 5 at LIQ_PH-ILD_00000852 (emphasis added).) As discussed above, the "new" indication is: "the treatment of pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3) to improve exercise ability." (Ex. 12 at UTC_PH-ILD_010745.) [redacted] (*See* Ex. 4 at 229:19-231:9.) Although this letter was filed after the '327 patent issued, it evidences Mr. Snader's ongoing understanding that the claims of the '793 patent cover the same subject matter as at least claim 1 of the '327 patent. Mr. Snader's willingness to inform other government agencies that the '793 patent claims cover improving exercise capacity in PH-ILD patients, but selectively withhold that same information during prosecution of the '327 patent, directed to the same subject matter, evidences his intent to deceive.[9]

UTC argues that the '793 patent was incorporated by reference "in its entirety" into the '327 patent, thereby excusing its failure to disclose the Asserted References. *See* D.I. 239 at 5. However, incorporating the '793 patent does not incorporate the Asserted References, which address the scope of the '793 patent claims. Also, the portion of the '327 patent that UTC cites as incorporating the '793 patent "in its entirety" merely addresses a type of inhalation delivery device: "Pulsed inhalation devices are disclosed, for example, in U.S. patent application publication No.

[9] UTC's FDA letter also underscores the materiality of the Asserted References.

20080200449, U.S. Pat. Nos. 9,358,240; 9,339,507; 10,376,525; and 10,716,793, each of which is incorporated herein by reference in its entirety." (*See* Ex. 19 ('327 patent) at 20:53-57.) The '793 patent was identified ***only*** for its disclosure of pulsed inhalation devices. Rather than evidencing a lack of intent, this surgical disclosure underscores Messrs. Snader's and Maebius' intent to deceive because they told the PTO that the '793 patent was relevant for its disclosure of a delivery device and withheld the fact that its claims encompass improving exercise capacity in PH-ILD patients.

When viewed in the light most favorable to Liquidia, a factfinder could find that the single most reasonable inference is that Messrs. Maebius and Snader intended to deceive the PTO. At the very least, the evidence creates a genuine dispute of material fact regarding intent, precluding summary judgment.

IV. CONCLUSION

Liquidia respectfully requests that the Court deny UTC's request to file summary judgment during the pendency of expert discovery and instead, if inclined to hear summary judgment, adopt Liquidia's compromise proposal: (1) both parties be permitted to file a MSJ, (2) MSJs be filed after the close of expert discovery, and (3) oral argument on summary judgment, if requested, be held at the pre-trial conference or a mutually agreed-upon date.

/s/ Nathan R. Hoeschen
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Dated: January 23, 2025

CERTIFICATE OF SERVICE

I hereby certify that on January 23, 2025, this document was served on DG-ILD@goodwinlaw.com, UTCvLiquidia-Del-23cv975@mwe.com and the persons listed below in the manner indicated:

BY EMAIL

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EXHIBIT 1

Habibi, John A

From: Habibi, John A
Sent: Thursday, January 9, 2025 11:35 AM
To: Jackson, William C; Sukduang, Sanya; z/Liquidia v UTC 308970-201; kkeller@shawkeller.com; nhoeschen@shawkeller.com
Cc: DG-ILD; UTCvLiquidia-Del-23cv975; mflynn@morrisnichols.com
Subject: RE: Leave to file Motion for Summary Judgment

Hi William,

As you will see from the email chain, Liquidia asked UTC for more details regarding its proposal for summary judgment, including a proposed schedule, as well as the fact the UTC raised SJ on inequitable conduct for the first time this week. UTC did not respond, and instead withheld its proposed SJ timing until the meet and confer. While you asked for "views/thoughts/ideas in the interim," UTC failed to provide the same. It is evident that UTC had no intent to meaningfully engage in a meet and confer process to reach a compromised position. Instead, as is clear from the email chain, UTC determined that it would file its motion for leave regardless of Liquidia's response. The ability to say that you discussed with UTC, in advance, our compromise are unverifiable and a last minute attempt to justify UTC's haste, as evident by the fact that during the meet and confer you never mentioned your "pre-discussion" with UTC.

Your last sentence does not satisfy our inquiry in the last paragraph of our email. As the Scheduling Order makes clear:

10. Case Dispositive Motions. No case dispositive motions shall be filed without leave of Court.
11. Applications by Motion. Except as otherwise specified herein, any application to the Court shall be by written motion. Any non-dispositive motion should contain the statement required by Local Rule 7.1.1.

If UTC is filing a "motion" as it appears to indicate, then UTC is in agreement that Liquidia has 14 days to respond.

Regards,
John Habibi

John Habibi
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jhabibi@cooley.com

From: Jackson, William C <WJackson@goodwinlaw.com>
Sent: Thursday, January 9, 2025 10:57 AM
To: Habibi, John A <JHabibi@cooley.com>; Sukduang, Sanya <ssukduang@cooley.com>; z/Liquidia v UTC 308970-201 <zLiquidiavUTC308970201@cooley.com>; kkeller@shawkeller.com; nhoeschen@shawkeller.com
Cc: DG-ILD <DG-ILD@goodwinlaw.com>; UTCvLiquidia-Del-23cv975 <UTCvLiquidia-Del-23cv975@mwe.com>; mflynn@morrisnichols.com
Subject: RE: Leave to file Motion for Summary Judgment

[External]

John:

Thank you for your email.

The counterproposals that Liquidia made at the meet and confer were the types of information I had sought in advance – i.e. in my email immediately below yours in this email chain, in which I asked Liquidia to "share any views/thoughts/ideas" in advance of the meet and confer this morning. Rather than doing so, Liquidia chose to withhold those proposed conditions until the call this morning. Nevertheless, in advance of the call, we discussed and confirmed with the client that the types of conditions that Liquidia ultimately identified would be unacceptable. Therefore, a call to the client to confirm our disagreement with those conditions was unnecessary. And your suggestion that we had to further consult our client is precisely the sort of delay tactic I had previously identified as concerning.

As we explained on the call this morning, we intend to file a motion for leave consistent with the Scheduling Order in this matter, and submit a letter brief in support of that motion. I trust this fully addresses the matter in the last paragraph of your email.

William C Jackson

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From: Habibi, John A <JHabibi@cooley.com>
Sent: Thursday, January 9, 2025 10:01 AM
To: Jackson, William C <WJackson@goodwinlaw.com>; Sukduang, Sanya <ssukduang@cooley.com>; z/Liquidia v UTC 308970-201 <zLiquidiavUTC308970201@cooley.com>; kkeller@shawkeller.com; nhoeschen@shawkeller.com
Cc: DG-ILD <DG-ILD@goodwinlaw.com>; UTCvLiquidia-Del-23cv975 <UTCvLiquidia-Del-23cv975@mwe.com>; mflynn@morrisnichols.com
Subject: RE: Leave to file Motion for Summary Judgment

EXTERNAL
Counsel,

We write to memorialize the discussions held and Liquidia's proposal presented during the parties' January 9, 2025 meet and confer.

During the meeting, UTC indicated its intention to seek leave today to file a motion for summary judgment regarding Liquidia's claim of inequitable conduct. In the spirit of compromise, Liquidia indicated that it would not oppose UTC's motion for leave if UTC agreed to the following conditions:

1. Both parties would be permitted to file one motion summary judgment;
2. Motions for summary judgment would be filed after the close of expert discovery;
3. To the extent the Court seeks arguments on motions for summary judgment, such arguments would occur at the pre-trial conference or on a mutually agreed-upon date. Counsel for Liquidia also offered to consider a counter-proposal on the date for oral argument.

Without consulting its client, or offering to consider the proposal and further discuss a compromised position to present to the Court to avoid a motions practice, counsel for UTC declined this proposal and reiterated its intention to immediately proceed with filing its motion for leave. UTC also indicated it was retaining its right to file additional summary judgment motions and also file a responsive expert report during the course of expert discovery, addressing Liquidia's inequitable conduct claims.

During the meet and confer, UTC also did not provide any basis for filing a letter brief rather than a formal motion, as required by Paragraph 11 of the parties' Scheduling Order. Please confirm the basis for UTC's decision to proceed with a letter brief in lieu of the formal motion required by the Scheduling Order.

Regards,
John Habibi

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From: Jackson, William C <WJackson@goodwinlaw.com>
Sent: Tuesday, January 7, 2025 11:44 AM
To: Sukduang, Sanya <ssukduang@cooley.com>; z/Liquidia v UTC 308970-201 <zLiquidiavUTC308970201@cooley.com>; kkeller@shawkeller.com; nhoeschen@shawkeller.com
Cc: DG-ILD <DG-ILD@goodwinlaw.com>; UTCvLiquidia-Del-23cv975 <UTCvLiquidia-Del-23cv975@mwe.com>; mflynn@morrisnichols.com
Subject: RE: Leave to file Motion for Summary Judgment

[External]

We will send an invite for Thursday at 9am.

Do you think you could share any views/thoughts/ideas in the interim? Thanks.

William C Jackson

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From: Sukduang, Sanya <ssukduang@cooley.com>
Sent: Tuesday, January 7, 2025 11:31 AM
To: Jackson, William C <WJackson@goodwinlaw.com>; z/Liquidia v UTC 308970-201 <zLiquidiavUTC308970201@cooley.com>; kkeller@shawkeller.com; nhoeschen@shawkeller.com
Cc: DG-ILD <DG-ILD@goodwinlaw.com>; UTCvLiquidia-Del-23cv975 <UTCvLiquidia-Del-23cv975@mwe.com>; mflynn@morrisnichols.com
Subject: RE: Leave to file Motion for Summary Judgment

EXTERNAL
William,

We, and local counsel for Liquidia, are available on Thursday, before 11:00 AM, to confer on UTC's new request to file a summary judgment motion addressing inequitable conduct. If that time does not work, we can look for additional availability Friday.

Thanks
Sanya

From: Sukduang, Sanya <ssukduang@cooley.com>
Sent: Monday, January 6, 2025 7:17 PM
To: Jackson, William C <WJackson@goodwinlaw.com>; z/Liquidia v UTC 308970-201 <zLiquidiavUTC308970201@cooley.com>; kkeller@shawkeller.com; nhoeschen@shawkeller.com
Cc: DG-ILD <DG-ILD@goodwinlaw.com>; UTCvLiquidia-Del-23cv975 <UTCvLiquidia-Del-23cv975@mwe.com>; mflynn@morrisnichols.com
Subject: Re: Leave to file Motion for Summary Judgment

Your false narrative falls flat.

UTC does not dispute that today was the first day it has raised summary judgment. We are not seeking delay. We are seeking to consult with Liquidia on an issue UTC raised for the first time this afternoon without any details.

If UTC wants to file a request without permitting us to consult with Liquidia and without actually meeting and conferring on UTC's request and proposed motion, UTC can do so. The record is clear and UTC is seeking to circumvent the rules under the false allegation that Liquidia is seeking to delay.

Sanya

From: Jackson, William C <WJackson@goodwinlaw.com>
Sent: Monday, January 6, 2025 7:09:56 PM
To: Sukduang, Sanya <ssukduang@cooley.com>; z/Liquidia v UTC 308970-201 <zLiquidiavUTC308970201@cooley.com>; kkeller@shawkeller.com <kkeller@shawkeller.com>; nhoeschen@shawkeller.com <nhoeschen@shawkeller.com>
Cc: DG-ILD <DG-ILD@goodwinlaw.com>; UTCvLiquidia-Del-23cv975 <UTCvLiquidia-Del-23cv975@mwe.com>; mflynn@morrisnichols.com <mflynn@morrisnichols.com>
Subject: RE: Leave to file Motion for Summary Judgment

[External]

Sanya:

Thank you for your email, but I was not being sarcastic.

You do not dispute the fact that we have repeatedly discussed these issues. And you also do not dispute the fact that we requested that Liquidia withdraw its groundless inequitable conduct claims on multiple occasions, including the November 21 meet and confer. And Liquidia has consistently refused to do so. Evidently the only issue you now contend we haven't discussed is the actual summary judgment motion itself. We disagree – we believe we addressed these issues on the November 21 meet and confer, as noted in my original email below.

Your stance that you will respond "this week" is merely another effort to delay. We believe we can certify that "reasonable efforts have been made to reach agreement on the subject of this motion" because we have repeatedly raised it and you have told us that Liquidia is unwilling to withdraw its inequitable conduct claims. But, again, to the degree you want to have any further communications beyond the exchanges to date on these issues, we are available at any time tomorrow.

William C Jackson

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From: Sukduang, Sanya <ssukduang@cooley.com>
Sent: Monday, January 6, 2025 6:34 PM
To: Jackson, William C <WJackson@goodwinlaw.com>; z/Liquidia v UTC 308970-201 <zLiquidiavUTC308970201@cooley.com>; kkeller@shawkeller.com; nhoeschen@shawkeller.com
Cc: DG-ILD <DG-ILD@goodwinlaw.com>; UTCvLiquidia-Del-23cv975 <UTCvLiquidia-Del-23cv975@mwe.com>; mflynn@morrisnichols.com
Subject: Re: Leave to file Motion for Summary Judgment

EXTERNAL
William,

Your sarcasm is not well taken.

At no time did UTC meet and confer regarding summary judgment and your unsupported request that Liquidia drop its inequitable conduct positions are unrelated to filing summary judgment in a Delaware Hatch-Waxman case.

You are asking for our position. We need to address the request with Liquidia.

The variety of reasons include, but not limited to:
UTC's late afternoon demand for a response or a meet and confer the same day.

UTC's failure to raise summary judgment until today.

The weather issues in DC that have impacted power.

The need to address this newly raised issue with Liquidia and their need to address internally.

Prematurity of the issue as UTC has not provided its expert response, if any.

The lack of summary judgment timing proposal.

As I noted today, we will respond this week. UTC is, of course, able to submit its request without complying with the local rules. We cannot stop you.

Sanya

From: Jackson, William C <WJackson@goodwinlaw.com>
Sent: Monday, January 6, 2025 6:20:23 PM
To: Sukduang, Sanya <ssukduang@cooley.com>; z/Liquidia v UTC 308970-201 <zLiquidiavUTC308970201@cooley.com>; kkeller@shawkeller.com <kkeller@shawkeller.com>; nhoeschen@shawkeller.com <nhoeschen@shawkeller.com>
Cc: DG-ILD <DG-ILD@goodwinlaw.com>; UTCvLiquidia-Del-23cv975 <UTCvLiquidia-Del-23cv975@mwe.com>; mflynn@morrisnichols.com <mflynn@morrisnichols.com>
Subject: RE: Leave to file Motion for Summary Judgment

[External]

Sanya:

We are surprised that a snowstorm in Washington, D.C. would inhibit lawyers from a law firm as sophisticated as Cooley from responding to our email request, and/or (to the degree Liquidia thinks there is anything further to discuss) to meet and confer via telephone or zoom. You state that it is "not possible for a variety of reasons" but fail to identify even one. In light of counsels' numerous meet and confers in the past – almost always via zoom from locations other than the law firms' offices – we thought this was a rather simple request. Nor is it a heavy lift: we are merely asking whether you oppose us filing a letter with the Court seeking leave to file a summary judgment motion.

We believe we more than met and conferred on these issues, including when we met and conferred on Liquidia's groundless inequitable conduct counterclaims on November 21. We have asked Liquidia to withdraw those counterclaims on multiple occasions. And Liquidia has steadfastly refused. We do not think there is anything more to discuss or anything more for Liquidia to consider.

We reiterate our request to let us know by noon tomorrow whether you oppose our request for leave to file a summary judgment motion. And, to the degree Liquidia believes a meet and confer is necessary, please identify a time when you are available tomorrow morning for such a call or zoom.

William C Jackson

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From: Sukduang, Sanya <ssukduang@cooley.com>
Sent: Monday, January 6, 2025 5:47 PM
To: Jackson, William C <WJackson@goodwinlaw.com>; z/Liquidia v UTC 308970-201 <zLiquidiavUTC308970201@cooley.com>; kkeller@shawkeller.com; nhoeschen@shawkeller.com
Cc: DG-ILD <DG-ILD@goodwinlaw.com>; UTCvLiquidia-Del-23cv975 <UTCvLiquidia-Del-23cv975@mwe.com>; mflynn@morrisnichols.com
Subject: RE: Leave to file Motion for Summary Judgment

EXTERNAL
Counsel,

As you are aware, we are dealing with a winter storm on the East coast. You sent your email at 2:17 PM EST, demanding an immediate response or a meet and confer today. That's not possible for a variety of reasons. Moreover, we do not believe the parties ever conferred on a request to file summary judgment by UTC on any issue, let alone inequitable conduct.

We are addressing your request with Liquidia and will provide a response this week and if needed, schedule a meet and confer.

Thanks
Sanya

From: Jackson, William C <WJackson@goodwinlaw.com>
Sent: Monday, January 6, 2025 5:42 PM
To: Sukduang, Sanya <ssukduang@cooley.com>; z/Liquidia v UTC 308970-201 <zLiquidiavUTC308970201@cooley.com>; kkeller@shawkeller.com; nhoeschen@shawkeller.com
Cc: DG-ILD <DG-ILD@goodwinlaw.com>; UTCvLiquidia-Del-23cv975 <UTCvLiquidia-Del-23cv975@mwe.com>; mflynn@morrisnichols.com
Subject: RE: Leave to file Motion for Summary Judgment

[External]

Counsel for Liquidia:

As noted below, we believe the parties have more than satisfied their meet and confer obligations with respect to dismissing Liquidia's counterclaims. To the degree Liquidia disagrees, please let us know immediately and identify a time before noon tomorrow to meet and confer. And, as requested below, please let us know whether you oppose our request for leave to file a summary judgment motion on Liquidia's inequitable conduct counterclaims.

William C Jackson

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From: Jackson, William C
Sent: Monday, January 6, 2025 2:16 PM
To: 'Sukduang, Sanya' <ssukduang@cooley.com>; z/Liquidia v UTC 308970-201 <zLiquidiavUTC308970201@cooley.com>; kkeller@shawkeller.com; nhoeschen@shawkeller.com
Cc: DG-ILD <DG-ILD@goodwinlaw.com>; UTCvLiquidia-Del-23cv975 <UTCvLiquidia-Del-23cv975@mwe.com>; mflynn@morrisnichols.com
Subject: Leave to file Motion for Summary Judgment

Counsel,

Liquidia has doggedly pursued claims of inequitable conduct against UTC's employees and counsel despite there being no factual basis that could conceivably meet the exacting *Therasense* legal standard. Because there are no facts in this case upon which a reasonable fact finder could find in favor of Liquidia, UTC intends to seek leave from the Court to file a summary judgment motion to dispose of Liquidia's inequitable conduct claims as we discussed on the meet-and-confer on November 21.

Please confirm whether Liquidia will immediately withdraw all allegations of inequitable conduct. If not, please confirm by the end of the day today whether Liquidia intends to oppose UTC's motion for leave, or provide a time today when you are available to meet and confer.

William C Jackson

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EXHIBIT 2

Habibi, John A

From: Sukduang, Sanya
Sent: Monday, January 13, 2025 4:24 PM
To: Jackson, William C; Flynn, Michael J.; Dcarsten@mwe.com; aburrowbridge@mwe.com; Adykhuis@mwe.com
Cc: kkeller@shawkeller.com; Nate Hoeschen; z/Liquidia v UTC 308970-201; UTCvLiquidia-Del-23cv975; DG-ILD
Subject: Re: Activity in Case 1:23-cv-00975-RGA-SRF United Therapeutics Corporation v. Liquidia Technologies, Inc. Set Answering Brief Deadline

William:

It is clear the parties disagree. It is unfortunate UTC is unwilling to compromise.

We will file our opposition in due course.

Thanks
Sanya

From: Jackson, William C <WJackson@goodwinlaw.com>
Sent: Monday, January 13, 2025 3:58:04 PM
To: Sukduang, Sanya <ssukduang@cooley.com>; Flynn, Michael J. <mflynn@morrisnichols.com>; Dcarsten@mwe.com <Dcarsten@mwe.com>; aburrowbridge@mwe.com <aburrowbridge@mwe.com>; Adykhuis@mwe.com <Adykhuis@mwe.com>
Cc: kkeller@shawkeller.com <kkeller@shawkeller.com>; Nate Hoeschen <nhoeschen@shawkeller.com>; z/Liquidia v UTC 308970-201 <zLiquidiavUTC308970201@cooley.com>; UTCvLiquidia-Del-23cv975 <UTCvLiquidia-Del-23cv975@mwe.com>; DG-ILD <DG-ILD@goodwinlaw.com>
Subject: RE: Activity in Case 1:23-cv-00975-RGA-SRF United Therapeutics Corporation v. Liquidia Technologies, Inc. Set Answering Brief Deadline

[External]

Sanya:

We disagree with your proposal. At the outset, however, we note that this is not a request to modify the schedule. This is merely a request for leave to file a summary judgment motion, similar to Docket No. 224 in the original action, in which Liquidia sought leave to file a summary judgment motion. Liquidia was not seeking to modify the schedule there, nor is UTC seeking to do so here.

As we noted several times during the meet and confer process before we filed our letter motion, we do not believe that Liquidia has any factual or legal basis to continue to assert the inequitable conduct claims. And that will not change between now and the conclusion of expert discovery, let alone between now and the pretrial conference or trial. In fact, we have already written you a Rule 11 letter noting that you have no basis to continue to pursue those claims.

While we expected you to oppose the summary judgment motion itself, we are surprised that you are opposing our request for leave to file the motion identified to you and addressed in our letter. We think the parties and the Court

would be better served by understanding sooner rather than later whether those claims are in the case. If there is no factual or legal basis for those claims (as we explain in our letter), continuing to spend time on them is a waste of the Court's and the parties' time.

We reiterate our request that you consent to our request for leave.

William C Jackson

GOODWIN

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From: Sukduang, Sanya <ssukduang@cooley.com>
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Cc: kkeller@shawkeller.com; Nate Hoeschen <nhoeschen@shawkeller.com>; z/Liquidia v UTC 308970-201 <zLiquidiavUTC308970201@cooley.com>
Subject: FW: Activity in Case 1:23-cv-00975-RGA-SRF United Therapeutics Corporation v. Liquidia Technologies, Inc. Set Answering Brief Deadline

EXTERNAL
Counsel,

In light of the briefing schedule set forth by the Court with respect to UTC's motion to seek leave to file SJ, and UTC's failure to establish, let alone mention, good cause to justify its schedule modification, we again request UTC consider our proposal for SJ briefing.

It is more than likely the Court outright denies UTC's request. And at most, if it is granted, it will likely follow the schedule we proposed during the meet and confer, given the current schedule for briefing. We believe that it is in the best interest of both parties, as well as reducing burden on the Court, for UTC to withdraw its motion and the parties file a joint request for SJ briefing with the following schedule:

1. Both parties file 1 SJ motion each;
2. SJ motions are filed after the close of expert discovery; and
3. Oral argument, to the extent requested, will be at the pre-trial conference or a time agreed to by the parties and the Court.

While we understand UTC's request to have SJ heard as soon as possible, that desire seems implausible at this point and coming to an agreement serves multiple purpose.

Please let us know by 3:00 PM tomorrow, January 14, if UTC will agree. If you would like to further confer on this issue, please let us know.

Thanks
Sanya

From: ded_nefreply@ded.uscourts.gov <ded_nefreply@ded.uscourts.gov>
Sent: Friday, January 10, 2025 1:32 PM
To: ded_ecf@ded.uscourts.gov
Subject: Activity in Case 1:23-cv-00975-RGA-SRF United Therapeutics Corporation v. Liquidia Technologies, Inc. Set Answering Brief Deadline

[External]

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U.S. District Court

District of Delaware

Notice of Electronic Filing

The following transaction was entered on 1/10/2025 at 1:32 PM EST and filed on 1/9/2025
Case Name: United Therapeutics Corporation v. Liquidia Technologies, Inc.
Case Number: 1:23-cv-00975-RGA-SRF
Filer:
Document Number: No document attached

Docket Text:
Set Answering Brief Deadline re [238] MOTION for Leave to File Motion for Summary Judgment. Answering Brief/Response due date per Local Rules is 1/23/2025. (nms)

1:23-cv-00975-RGA-SRF Notice has been electronically mailed to:

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1:23-cv-00975-RGA-SRF Filer will deliver document by other means to:

EXHIBIT 3

[redacted]

IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

UNITED THERAPEUTICS CORPORATION,

Plaintiff,

v.

C.A. No. 23-975-RGA-SRF

LIQUIDIA TECHNOLOGIES, INC.,

Defendant.

_____

[redacted]

October 31, 2024

9:05 a.m. EDT

Videotaped deposition of STEPHEN B. MAEBIUS, held at the offices of Goodwin Procter LLP, 2900 N Street, N.W., Washington, D.C., before Misty Klapper, Registered Merit Reporter, Certified Realtime Reporter, Certified Shorthand Reporter and Notary Public.

Mr. -- Mr. Maebius.

MR. SUKDUANG: And what should be Maebius Number 2 should be a patent. And for the record, it's U.S. Patent Number 11,826,327.

(Thereupon, Maebius Deposition Exhibit Number 2 was marked for identification.)

BY MR. SUKDUANG:

[redacted]

[redacted]

Q. Okay. And is this a patent that Foley & Lardner -- Lardner prosecuted for UTC?

A. Yes.

Q. And were you involved in the prosecution of the '327 patent for UTC?

A. Yeah.

Q. Other than yourself, who at Foley was involved in the prosecution of the '327 patent?

this provisional application?

MR. JACKSON: I'm going to instruct you not to answer on the grounds of privilege.

BY MR. SUKDUANG:

Q. Are you going to follow your instruction?

A. Yeah.

[redacted]

MR. JACKSON: Objection to form and calls for a legal conclusion.

You can answer if you can.

[redacted]

BY MR. SUKDUANG:

[redacted]

MR. JACKSON: Same objection.

[redacted]

///

BY MR. SUKDUANG:

[redacted]

MR. JACKSON: Same objection.

[redacted]

BY MR. SUKDUANG:

[redacted]

MR. JACKSON: Same objection.

[redacted]

BY MR. SUKDUANG:

[redacted]

MR. JACKSON: Objection, calls

for a legal conclusion.

BY MR. SUKDUANG:

Q. Let me ask it a different way.

You understand during prosecution requests for extensions of time can be filed, correct?

A. Yeah.

Q. And you can file a request for an extension of time without actually filing a response to the office action; is that correct?

A. Yeah.

Q. Okay. So I don't want to talk about filing for extensions of time. I want to talk about actual substantive responses to office actions.

Do you understand that?

A. Yes.

Q. And do you understand what I'm talking about?

A. (Nodding.)

Q. Yes?

A. Yes.

Q. Okay. When I prosecuted, I called it responses to office actions.

Is that what you call it?

A. Yes, a substantive response.

Q. Okay.

MS. REPORTER: I'm sorry?

THE WITNESS: Substantive response, sure.

BY MR. SUKDUANG:

[redacted]

MR. JACKSON: Objection, calls for a legal conclusion.

[redacted]

BY MR. SUKDUANG:

Q. Okay. Once an application is allowed by the patent office, an issue fee will be due, correct?

A. Yeah.

A. Yeah.

Q. Okay. In the '793 patent IPR petition identified in C276, that's the same patent -- '793 patent we discussed earlier, correct?

A. Yeah.

Q. Okay. And this IPR petition -- excuse me -- this IPR proceeding for this '793 patent, you were the lead counsel for United Therapeutics, correct?

A. Yeah.

[redacted]

MR. JACKSON: I'm going to instruct you not to answer on the grounds of privilege.

BY MR. SUKDUANG:

Q. Are you going to follow that instruction?

A. Yeah.

[redacted]

reason.

[redacted]

MR. JACKSON: I'm going to have you exclude from your answer any analysis you performed for UTC or communications you had with UTC on that question.

To the degree you can answer still, I'll let you answer.

[redacted]

BY MR. SUKDUANG:

Q. Can you go to the page -- could you -- ready?

Could you go to the page ending in 9723 for me.

A. Yeah.

Q. Do you see a line C121?

A. Yeah.

Q. And this document submitted in

Q. Okay. In this section regarding long-felt need, you and UTC are arguing that the claims of the '793 patent meet the need of treating pulmonary hypertension associated with interstitial lung disease, correct?

A. That's one of the arguments, yeah.

Q. Okay. You understand this '327 patent is also directed to treating pulmonary hypertension associated with interstitial lung disease?

MR. JACKSON: Objection, form, misstates, calls for a legal conclusion.

And I instruct you to exclude from your answer any analysis or communications you had with UTC about the '327 patent and what it covers or doesn't cover.

THE WITNESS: The -- the claim language does include pulmonary hypertension associated with

interstitial lung disease.

BY MR. SUKDUANG:

Q. And in this response, patent owner's response, you actually submit the 2021 Tyvaso label, correct?

A. Yeah.

Q. And -- and in submitting the 2021 Tyvaso label, you're informing the patent office that this is the indication that the '793 patent covers, correct?

A. Yes. We're saying this is evidence of a long-felt unmet need being satisfied in the case of '793.

Q. Okay. And the long-felt need is the indications identified in the 2021 Tyvaso label, correct?

A. Yes, to provide a better treatment for those patients.

Q. Okay. So if the Tyvaso label said treatment of gout, that would not be something you'd be pointing to with respect to the '793 patent, correct?

Let me say that better.

You know there's an application -- the -- the '793 patent -- let me make this even easier.

Let me have the '793 patent.

MR. SUKDUANG: Could you pass that over.

(Thereupon, Maebius Deposition Exhibit Number 11 was marked for identification.)

BY MR. SUKDUANG:

Q. Mr. Maebius, I've provided you as Exhibit 11 U.S. Patent Number 10,716,793. This is the '793 patent we've been talking about today?

A. Yeah.

Q. And you prosecuted this patent application for UTC, correct?

A. Yes.

Q. And this is the '793 patent that's involved in the IPR we've been discussing that you were lead counsel of?

A. Yeah.

Q. Okay. Now, you see that there's an application that was filed on January 31st 2020?

A. Yeah.

Q. And that was application number 16/778662?

A. Yeah.

Q. And your understanding is that the '662 application was the application that -- that gave direct rise to the issued '793 patent?

A. Yeah.

Q. Okay. Do you know whether there are any continuations or CIPs or divisionals stemming from the '662 patent itself -- excuse me -- '662 application itself?

A. I don't know how the -- the branches connect, but there are pending applications in that family.

Q. Okay. So whether it's the '662 application itself or the applications that

CERTIFICATE OF NOTARY

I, MISTY KLAPPER, the officer before whom the foregoing deposition was taken, do hereby certify that the witness whose testimony appears in the foregoing deposition was duly sworn by me; that the testimony of said witness was taken by me in shorthand and thereafter reduced to typewriting by me; that said deposition is a true record of the testimony given by said witness; that I am neither counsel for, related to, nor employed by any of the parties to the action in which this deposition was taken; and, further, that I am not a relative or employee of any attorney or counsel employed by the parties hereto, nor financially or otherwise interested in the outcome of this action.

Misty Klapper, RMR, CRR, CSR

Notary Public

EXHIBIT 4

[redacted]

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

UNITED THERAPEUTICS CORPORATION,	)	
Plaintiff,	)	Case No. 23-975
vs.	)	(RGA)(SRF)
LIQUIDIA TECHNOLOGIES, INC.,	)	
Defendant.	)	

Tuesday, November 26, 2024
9:34 a.m.

Remote Zoom Videotaped Deposition of SHAUN SNADER, held before Stacey L. Daywalt, a Court Reporter and Notary Public of the District of Columbia.

[redacted]

MR. JACKSON: Objection, form and calls for a legal conclusion.

[redacted]

BY MR. DAVIES:

[redacted]

[redacted]

MR. JACKSON: Objection, form.

[redacted]

BY MR. DAVIES:

[redacted]

MR. JACKSON: Objection, mischaracterizes.

[redacted]

BY MR. DAVIES:

[redacted]

MR. JACKSON: Objection, form and calls for a legal conclusion.

[redacted]

BY MR. DAVIES:

[redacted]

MR. JACKSON: Same objection.

[redacted]

BY MR. DAVIES:

[redacted]

MR. JACKSON: Objection, form.

[redacted]

BY MR. DAVIES:

[redacted]

MR. JACKSON: Objection, form.

[redacted]

Q. Can you turn to the Exhibit 3, Mr. Snader.

That should be the '793 patent.

A. I have Exhibit 3 open.

Q. Okay. Great.

[redacted]

MR. JACKSON: I'm going to instruct the witness not to answer on the grounds it involves the attorney-client privilege.

Q. Are you going to follow your counsel's advice, Mr. Snader?

A. This time and every time.

Q. Okay.

[redacted]

MR. JACKSON: Instruct the witness not to answer on the grounds it involves the attorney-client privilege.

Q. Are you going to follow your attorney's advice?

A. This time and every time.

MR. JACKSON: Okay. I'm not sure whether this involves the attorney-client privilege or not.

So I'm going to instruct you to exclude from your answer, Mr. Snader, [redacted]

BY MR. DAVIES:

[redacted]

MR. JACKSON: Going to instruct you not to answer on the ground it involves the attorney-client and attorney work product privileges.

BY MR. DAVIES:

[redacted]

MR. JACKSON: I'll let you answer the question a yes, no or I don't recall, as

long as Mr. Davies agrees that it's not a waiver.

MR. DAVIES: Agreed.

[redacted]

BY MR. DAVIES:

[redacted]

MR. JACKSON: That I'm not going to let you answer on the grounds it involves the attorney-client and attorney work product privileges.

BY MR. DAVIES:

Q. Mr. Snader, I'm going to enter another document here as Exhibit 7 that hopefully you should be able to see shortly.

(Exhibit 7, Patent Owner's Mandatory Notices Under 37 CFR Section 42.8, LIQ_PH-ILD_00101713-718, marked for identification.)

Q. Exhibit 7 is Patent Owner's Mandatory Notices Under 37 CFR Section 42.8 that was submitted in the '793 IPR. And it begins with production page LIQ_PH-ILD_0010713.

And just let me know once you're able to open Exhibit 7, Mr. Snader.

A. I have opened Exhibit 7.

Q. And Mr. Snader, what is Exhibit 7?

A. It is entitled Patent Owner's Mandatory Notices Under 37 CFR Section 42.8 and in connection with IPR2021-00406.

Q. And if you turn to what is numbered Page 3 of the mandatory notice.

Let me know once you're there.

A. (Complying.)

I'm there.

Q. Okay. And you were identified as backup counsel for Patent Owner United Therapeutics. Correct?

A. I am.

And I now realized I either screwed up my registration number on this one or I gave you my Virginia Bar number when you asked before.

Q. So is your USPTO registration number 59987?

A. Yes, I believe so.

[redacted]

[redacted]

(Exhibit 8, Decision Granting Institution of Inter Partes Review 35 USC Section 314, LIQ_PH-ILD_00101347-1390, marked for identification.)

Q. Mr. Snader, I'm going to enter another exhibit as Snader Exhibit 8, a document titled Decision Granting Institution of Inter Partes Review 35 USC Section 314 submitted in the '793 IPR and bearing beginning production

No. LIQ_PH-ILD_00101347.

And let me know once you have Exhibit 8 up, Mr. Snader.

A. I have Exhibit 8 open.

Q. And what is Exhibit 8?

A. It is entitled Decision Granting Institution of Inter Partes Review 35 USC Section 314 in connection with the IPR that we have been discussing.

[redacted]

MR. JACKSON: I'm going to instruct you not to answer on the ground that it involves the attorney-client and attorney work product privileges.

BY MR. DAVIES:

[redacted]

[redacted]

MR. JACKSON: I'll let you answer that question as yes, no or I don't recall.

[redacted]

MR. JACKSON: I'm willing to let him answer that question, Jonathan, so long as you agree it's not a waiver.

MR. DAVIES: That's fine.

MR. JACKSON: Okay.

[redacted]

BY MR. DAVIES:

Q. Okay. I'm going to enter as Snader Exhibit 9 a document titled Patent Owner Response from the '793 patent IPR.

(Exhibit 9, Patent Owner Response, LIQ_PH-ILD_00000110-184, marked for

an instruction.

When you were asking before, you were asking what the argument was, which is going to be a hit on attorney-client and attorney work product, but I'll --

(Simultaneous crosstalk.)

MR. DAVIES: Wait. Wait. The argument is presented in a public document.

I don't even understand the basis for your objections, William.

BY MR. DAVIES:

[redacted]

MR. JACKSON: Shaun, that's a do you know whether.

I'll let you answer the question as asked.

[redacted]

BY MR. DAVIES:

[redacted]

MR. JACKSON: Again, you're asking what the basis for an argument is.

That's a legal analysis. Right?

I'm not going to let him answer the question involving legal analysis, because I don't want you to hit -- I don't want you -- you guys have made a variety of motions before the Court trying to get a variety of things that I think are wrong and improper, and so far the Court has agreed with us every time.

And I don't want you to take this as a waiver, so I'm going to make sure we don't waive.

So I'm not going to let him answer the question as asked.

MR. DAVIES: I disagree that my question invokes any waiver.

BY MR. DAVIES:

Q. Mr. Snader, do you agree that United Therapeutics presented its position and arguments as to why the '793 patent satisfied a long felt but unmet need in the treatment of pulmonary hypertension in its Patent Owner Response beginning on Page 61?

MR. JACKSON: I'll let you answer that question as asked.

THE WITNESS: United Therapeutics' arguments in its Patent Owner Response addressing the issue of long felt unmet need do appear on Pages 61 through 62 of the Patent Owner Response.

BY MR. DAVIES:

Q. And as written on Pages 61 and 62 of the Patent Owner Response, it's correct that United Therapeutics cited to and relied on the approval of inhaled treprostinil in PH-ILD in support of its long felt but unmet need presented in its Patent Owner Response. Correct?

MR. JACKSON: I'm going to let you answer that question as asked.

THE WITNESS: I'm not sure of the distinguishing point between "cited to" and "relied upon."

But yes, in this section addressing long felt unmet need, the use of inhaled treprostinil for treatment of PH-ILD is addressed as part of that argument.

BY MR. DAVIES:

Q. Mr. Snader, I'm going to enter as Exhibit 10 a document titled Declaration of Aaron Waxman, MD, Ph.D. from the '793 IPR produced at LIQ_PH-ILD_00102032.

And just let me know once you have that up.

(Exhibit 10, Declaration of Aaron Waxman, MD, Ph.D., LIQ_PH-ILD_00102032-2087, marked for identification.)

THE WITNESS: I have Exhibit 10 opened.

Q. And Mr. Snader, what is Exhibit 10?

A. The first page is titled Declaration of Aaron Waxman, MD, Ph.D., with the case caption of the '793 patent IPR.

[redacted]

[redacted]

MR. JACKSON: Objection, form and calls for a legal conclusion.

[redacted]

BY MR. DAVIES:

[redacted]

MR. JACKSON: That's a do you know whether.

And I'll let you answer the question as asked.

[redacted]

BY MR. DAVIES:

[redacted]

MR. JACKSON: Again, that's do you

perhaps my recollection is wrong about that. I don't really know.

But if you like, I'll move on to Exhibit 12 now.

Q. Yep.

[redacted]

Q. Do you have Exhibit 12?

A. I do.

Q. And what is Exhibit 12?

A. According to the front page, it is Paper 78 in the IPR proceeding that we've been talking about. And it is the Judgment Final Written Decision Determining All Claims Unpatentable, 35 USC Section 318(a).

[redacted]

[redacted]

MR. JACKSON: Object to the form.

[redacted]

Q. And it was issued on July 19, 2022 according to the document. Is that correct?

A. I'm sorry. Can you repeat your question, please.

Q. Yeah. I'm sorry.

It was issued by the PTAB on July 19th, 2022. Correct?

A. I don't recall that, but I see that that's the date on the top right-hand corner of Exhibit 12.

Q. Do you know whether you considered

[redacted]

Q. Anything else?

A. No.

Q. Okay.

A. I have Exhibit 28 open.

[redacted]

Q. And Mr. Snader, I apologize if I already asked this.

[redacted]

MR. JACKSON: Again, I'm going to give you a little bit of leeway. I want to be very careful about how far we go.

But I'll allow the witness to answer the question as asked.

[redacted]

BY MR. DAVIES:

Q. Turning back to Exhibit 28.

Do you have Exhibit 28 in front of you?

A. I do.

Q. And what is Exhibit 28, if you know?

A. It is a -- based on what I'm reading here on the first page, it's a letter from Hyman, Phelps & McNamara dated February 12th, 2024 on behalf of its client United Therapeutics Corporation.

[redacted]

[redacted]

MR. JACKSON: So again, Mr. Davies, in the e-mail from Robert Min dated Thursday, September 19th, your colleague represented that you intend to depose Mr. Snader with respect to issues related to Liquidia's inequitable conduct counterclaim.

This is a document that's dated after the counterclaim was filed. It's dated February 12th, 2024. It's not to the Patent Office and it's not -- it was after the patent was obviously issued. So it can't relate to the inequitable conduct counterclaim.

I'll give you a little leeway here, but not much.

MR. DAVIES: Right. I disagree.

BY MR. DAVIES:

Q. Can you answer my question, Mr. Snader.

A. Can you repeat the question, please.

Q. One second.

[redacted]

[redacted]

[redacted]

MR. JACKSON: Again, same -- going to give you a little leeway, but not much.

[redacted]

BY MR. DAVIES:

[redacted]

MR. JACKSON: I'm going to instruct the witness not to answer on the grounds that that involves the attorney-client privilege and attorney work product doctrine.

BY MR. DAVIES:

Q. You're going to follow your attorney's instruction?

A. Yes.

Q. Okay. Can you go to Page 6 of this letter.

A. (Complying.)

I'm on Page 6.

Q. And I'm looking at the paragraph

that begins: "During the pendency of the 30-month stay for the PAH indication."

Do you see that?

A. I see that paragraph.

Q. Okay. And then there is a reference to an amendment that Liquidia made in the context of its 505(b)(2) NDA for Yutrepia.

Do you see that?

A. I do see a reference to an amendment.

Q. And then in this letter, it states: "In that amendment, Liquidia certified to the Orange Book patent information for Tyvaso and UTC timely sued Liquidia for patent infringement, but the subsequent litigation on the patents covering the new indication, the '793 patent and US Patent No. 11,826,327, the '327 patent, did not trigger a 30-month stay because those patents were added to the Orange Book for Tyvaso after the January 20, 2020 submission of the original Yutrepia 505(b)(2) NDA."

Do you see that statement?

A. I do.

Q. Is that a true statement?

MR. JACKSON: I'm going to make sure we're focusing on -- Jonathan, you're asking about the factual statement, not the legal implications of what -- you're not asking for legal implications, you're not asking for his -- any work product or attorney-client privilege.

You're just asking factually is that statement true.

BY MR. DAVIES:

Q. Is the statement that I just read in this letter submitted by United Therapeutics true?

(Simultaneous crosstalk.)

[redacted]

MR. JACKSON: Hold on.

Let me make sure we're focusing on the factual basis for the statement, not any legal analysis or legal conclusion drawn from the underlying facts.

BY MR. DAVIES:

Q. Can you answer, Mr. Snader.

MR. JACKSON: So fair enough.

I'm going to instruct the witness not to answer to the degree it involves any legal conclusion or a legal analysis that he has conducted.

Again, in -- before we started this deposition, we e-mailed you and asked, we understand that the deposition of Mr. Snader will be limited to the counterclaim for -- that Liquidia put forward on inequitable conduct. And that was a confirmation that we received.

So as a result, the deposition is limited to that.

You're unwilling to limit this question to the factual basis, and so I'm not going to let him answer any legal analysis or legal conclusion that was drawn from that.

MR. DAVIES: William, I think this is relevant.

And all I'm doing is reading a statement from a document that was submitted to the FDA by United Therapeutics [redacted] and I'm asking him if that is a true statement.

That's all I'm asking him. It's a

yes or no question.

BY MR. DAVIES:

Q. Are you willing to answer that question, Mr. Snader?

MR. JACKSON: So Mr. Snader, I'll -- to the degree you can answer to the factual piece underneath it, I will instruct you to exclude from your answer any legal analysis or legal conclusion or any attorney work product.

[redacted]

BY MR. DAVIES:

Q. Do you see the part of the statement that states that: "The patents covering the new indication"?

Do you see that?

A. Yes, I do.

Q. Do you know what the "new

indication" is that's being referred to there?

[redacted]

Q. And then this letter states that at least two of the patents covering that new indication on PH-ILD are the '793 patent and the '327 patent. Correct?

A. Yes, it identifies the '793 and the '327 patents.

Q. And it identifies those two patents as patents that cover the new indication, [redacted] Correct?

MR. JACKSON: Again, I'm going to instruct you to exclude from your answer any legal analysis or legal conclusion and any attorney work product.

If you can still answer within the scope of that, please do so.

THE WITNESS: I believe that that's -- that this sentence is referring to

those patents as, quote, "covering the new indication," end quote.

BY MR. DAVIES:

[redacted]

MR. DAVIES: Let's go off the record.

THE VIDEOGRAPHER: Please stand by. The time is 3:14 p.m. We're going off the record.

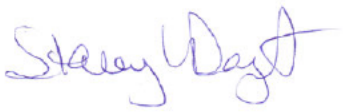
District of Columbia, to wit:

I, Stacey L. Daywalt, a Notary Public of the District of Columbia, do hereby certify that the within-named witness remotely appeared before me at the time and place herein set out, and after having been duly sworn by me, according to law, was examined by Counsel.

I further certify that the examination was recorded stenographically by me and this transcript is a true record of the proceedings.

I further certify that I am not of counsel to any of the parties, nor an employee of counsel, nor related to any of the parties, nor in any way interested in the outcome of this action.

As witness my hand and Notarial Seal this 2nd day of December, 2024.



Stacey L. Daywalt, Notary Public

My Commission Expires: 4/14/2026

EXHIBIT 5

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Re: NDA 213005 – YUTREPIA (Treprostinil) Inhalation Powder
Response to February 2, 2024 Letter from Liquidia Technologies, Inc.

Dear Ms. Dettelbach and Mr. Cooney:

On behalf of our client, United Therapeutics Corporation ("UTC"), we write in response to the letter dated February 2, 2024 from Liquidia Technologies, Inc. ("Liquidia") pertaining to its pending New Drug Application ("NDA") 213005 ("the YUTREPIA 505(b)(2) NDA") submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act ("FDC Act") and referencing UTC's TYVASO® (treprostinil) inhalation powder approved under NDA 022387. Ltr. from S. Lassman re Liquidia (Feb. 2, 2024) ("Liquidia Ltr.").

As UTC's December 29, 2023 letter explained, the U.S. Food and Drug Administration ("FDA" or "the Agency") erred in accepting Liquidia's attempt to amend its pending 505(b)(2) NDA because that course of action is foreclosed by FDA's

longstanding, consistently applied, and never-previously-challenged Bundling Rule. Ltr. from K. Karst re Liquidia (Dec. 29, 2023) ("UTC Ltr."). Accordingly, the UTC Letter requested that FDA comply with its Bundling Rule and past precedents by withdrawing—or directing Liquidia to withdraw—the YUTREPIA 505(b)(2) NDA amendment and requiring a new NDA submission.

Liquidia's letter provides no persuasive reason why this request should not be granted. Although it claims that the Bundling Rule is outdated and was superseded by rulemaking, the very same rulemaking materials cited in the Liquidia Letter expressly provide that FDA's Bundling Rule remains in full force and effect. Indeed, while the Liquidia Letter paints a picture of a new regulatory scheme permitting the addition of new indications to pending NDAs by way of amendment, that "new" regulatory scheme makes clear that the Bundling Rule remains very much in effect. With its convoluted explanation of FDA's Medicare Modernization Act of 2003 ("MMA") rulemakings, Liquidia encourages FDA to ignore more than 30 years of clear policy—policy directly cited in the very preambles enacting the rulemaking Liquidia relies upon—in a blatant attempt to circumvent both FDA's longstanding Bundling Rule and the 30-month stay provisions Congress enacted in order to provide for an orderly resolution of patent disputes prior to the approval of pending 505(b)(2) NDAs and Abbreviated New Drug Applications ("ANDAs").

Given the misleading nature of the Liquidia Letter and the continued relevance of the Bundling Rule, UTC reiterates that Liquidia wrongly submitted, and that FDA erred in accepting, Liquidia's amendment adding a new indication to its YUTREPIA 505(b)(2) NDA. For that reason, UTC continues to request that FDA require Liquidia to submit a new 505(b)(2) NDA to request approval of a new indication; certify to the patent information listed in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* ("Orange Book") as of the submission of that new NDA for any listed drug relied on for approval; and stay the approval of any new YUTREPIA 505(b)(2) NDA if there is timely filed patent infringement litigation in response to a notice of Paragraph IV certification to Orange Book-listed patent information.

I. BACKGROUND

A. Legal Background

The Drug Price Competition and Patent Term Restoration Act of 1984 (the "Hatch-Waxman Act" or "Hatch-Waxman"), Pub. L. No. 98-417, 98 Stat. 1585, amended the FDC Act to remove barriers to entry, increase availability of drugs, and reduce prescription

costs. *Serono Labs., Inc. v. Shalala*, 158 F.3d 1313, 1326 (D.C. Cir. 1998). In so doing, the Hatch-Waxman Act established an abbreviated pathway to market for drug products, including both duplicates and follow-on products, by allowing applicants to rely on FDA's findings of safety and effectiveness for other drug products—"listed drugs"—as the basis of approval. 21 U.S.C. § 355(j), (b)(2). Applicants submit either an ANDA or a 505(b)(2) NDA referencing a drug listed in the Orange Book with data "bridging" the proposed drug to the listed drug so that the applicant need not duplicate the extensive testing performed by the listed drug sponsor for approval. *Id.* This process allows more affordable drugs to come to market more quickly than if full studies for safety and effectiveness were required.

At the same time, however, the Hatch-Waxman Act recognized that many listed drugs are protected by valuable patents, and thus struck a balance between expediting follow-on product entry and respecting innovators' patent rights. To that end, Hatch-Waxman requires an NDA sponsor to file with FDA "the patent number and the expiration date of any patent which claims the drug . . . and with respect to which a claim of patent infringement could reasonably be asserted [against a competitor]," 21 U.S.C. § 355(b)(1); *see also* 21 C.F.R. § 314.50(h), and obligates FDA to "publish" and "make available to the public" a list of the patent data NDA holders have submitted to the Agency. 21 U.S.C. § 355(j)(7)(A)(i); *see also id.* § 355(c)(2). FDA publishes this patent information in the Orange Book. *Purepac Pharm. Co. v. Thompson*, 354 F.3d 877, 880 (D.C. Cir. 2004).

To speed the resolution of patent disputes between brands and follow-on sponsors so that competition can start as soon as the law permits, Congress required each ANDA or 505(b)(2) NDA relying on a listed drug to include "a certification . . . with respect to each [Orange Book-listed] patent which claims the listed drug . . . or . . . a use for such listed drug." 21 U.S.C. § 355(j)(2)(A)(vii); *see also* 21 C.F.R. § 314.53(f). Several patent certification types are available. *See* 21 U.S.C. § 355(j)(2)(A)(vii).

Paragraph IV certifications are particularly integral to the statutory and regulatory scheme. To help follow-on sponsors obtain certainty about a listed patent's coverage without subjecting them to the *in terrorem* threat of massive damages, the Patent Act deemed an applicant's submission of a Paragraph IV certification to FDA to be a "highly artificial" act of patent infringement that immediately can be litigated without subjecting the follow-on applicant to damages. 35 U.S.C. § 271(e); *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 678 (1990) ("Quite obviously, the purpose of [35 U.S.C. § 271](e)(2) and (e)(4) is to enable the judicial adjudication upon which the ANDA and paper NDA schemes depend."). Where an applicant submits a Paragraph IV certification in its original 505(b)(2) NDA, such notice must be provided "not later than 20 days after the date … [on]

which [FDA] informs the applicant that the application has been filed. *Id.* § 355(b)(3)(B)(i).

Because the whole point of Hatch-Waxman's patent-submission, patent-listing, Paragraph IV certification, and Paragraph IV notice provisions is to resolve patent disputes before FDA approval, the statute incentivizes brand manufacturers to sue as soon as they receive the legally-required notice. When the brand manufacturer sues within 45 days of receiving the legally-required notice, FDA may not approve the follow-on application until 30 months after the brand manufacturer receives the legally-required notice. 21 U.S.C. § 355(c)(3)(C). This 30-month stay permits the innovator and follow-on manufacturer to litigate all relevant patents prior to approval and market entry of the follow-on product. *Eli Lilly & Co. v. Teva Pharms. USA, Inc.*, 557 F.3d 1346, 1348-49 (Fed. Cir. 2009). A 30-month stay is available only with respect to patent information submitted to FDA before the date a 505(b)(2) NDA is submitted to the Agency, and typically only a single 30-month stay is available for each 505(b)(2) NDA containing a Paragraph IV certification. Ltr. to Gerald Masoudi, Docket No. FDA-2010-P-0223, at 5 (Oct. 19, 2010).

During the 30-month stay, FDA reviews the follow-on application. While a pending follow-on application may be amended during that review—or supplemented after approval—there are limits to such submissions. Specifically, the FDC Act states that "[a]n applicant may not amend or supplement an application . . . to seek approval of a drug that is a different drug that the drug identified in the application as submitted to the Secretary." 21 U.S.C. § 355(b)(4)(A). FDA has interpreted this provision to prohibit "an applicant from amending or supplementing a 505(b)(2) application to seek approval of a drug that has been modified to have a *different active ingredient, different route of administration, different dosage form, or certain differences in excipients* than the drug proposed in the original submission of the 505(b)(2) application," which "conforms with FDA's current policy regarding the types of proposed changes to a drug product that should be submitted as a separate application (see guidance for industry on 'Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees' (December 2004) [the '2004 Bundling Rule']." Abbreviated New Drug Applications and 505(b)(2) Applications, 81 Fed. Reg. 69580, 69635 (Oct. 6, 2016) (emphasis added). Conversely, the statute expressly permits the submission of an amendment or supplement to a pending NDA to seek approval for *a different strength*. 21 U.S.C. § 355(b)(4)(B).

No such permission is granted for a change in indication. Absent direction from Congress on the addition of a new indication to a pending 505(b)(2) NDA, FDA has interpreted its regulations such that "[m]ost requests for approval of a different indication or condition of use by a 505(b)(2) applicant should *not* be made as an amendment to the

505(b)(2) application," in accordance with the 2004 Bundling Rule. The 2004 Bundling Rule sets forth FDA's clear requirements for "what will be considered a separate marketing application." 2004 Bundling Rule, at 1. As explained in UTC's December 2023 letter, the Bundling Rule states:

> If submitted simultaneously in one application, requests for approval of different indications and uses for the same dosage form to be administered by the same route of administration . . . can be regarded, for the purposes of assessing user fees, as one application. . . . *After initial submission, a pending original or supplemental application should not be amended to add a new indication or claim*. . . . If the original application is not yet approved, *a request for approval of other new indications or claims should be submitted in a separate, original application*. If the initial application is approved, the application can be subsequently supplemented to add a new indication.

Id. at 4-5 (emphasis added). This Bundling Rule continues to be cited by the Agency in various documents, including, most recently, in a Standard Operating Procedures and Policies ("SOPP") publication dated *January 2024*. SOPP 8401 Administrative Processing of Original Biologics License Applications (BLA) and New Drug Applications (NDA), at 12 (Jan. 8, 2024) ("In limited circumstances, an applicant may submit two BLAs/NDAs for the same product that are concurrently reviewed as stand-alone applications with separate [Submission Tracking Numbers ('STNs')]. This occurs when an applicant has a pending BLA/NDA and seeks approval for another reason (for example a different indication or dosage) for the same product (refer to the [2004 Bundling Rule]")). Liquidia did not do this in their current application.

B. Factual Background

As UTC's December 2023 letter explained, UTC is the holder of five NDAs for drug products containing treprostinil, including TYVASO® (treprostinil) Inhalation Solution, 0.6 mg/mL, approved under NDA 022387. FDA initially approved TYVASO on July 30, 2009 for the treatment of Pulmonary Arterial Hypertension (WHO Group I) in patients with NYHA Class III symptoms, to increase walk distance (the "PAH Indication"). On March 31, 2021, FDA approved Supplement S-017 to the TYVASO NDA for a new indication: "for the treatment of pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3) to improve exercise ability" (the "PH-ILD Indication").

In January 2020, Liquidia submitted a 505(b)(2) NDA seeking approval of YUTREPIA (treprostinil) for the PAH Indication relying on UTC's TYVASO as the listed

drug. Liquidia's YUTREPIA 505(b)(2) NDA contained Paragraph IV certifications to some of the then-listed Orange Book patents for TYVASO, including, in particular, U.S. Patent Nos. 9,593,066 ("the '066 patent") and 9,604,901 ("the '901 patent"). UTC timely sued Liquidia for patent infringement, thereby triggering a 30-month stay on the approval of the YUTREPIA 505(b)(2) NDA that expired on or about October 24, 2022. Liquidia later amended its 505(b)(2) NDA and provided a Paragraph IV certification to a later-listed patent, U.S. Patent No. 10,716,793 ("the '793 patent"), but because that patent was later-listed, the Paragraph IV certification did not result in a 30-month stay. In May 2021, Liquidia responded to a Complete Response Letter ("CRL") from FDA resulting in an amendment to the YUTREPIA 505(b)(2) NDA and additional patent certifications. FDA tentatively approved the YUTREPIA 505(b)(2) NDA for the treatment of PAH, but, due to an ongoing 30-month stay, FDA could not grant final approval for the Liquidia 505(b)(2) NDA.

During the pendency of the 30-month stay for the PAH indication, UTC received approval of the new PH-ILD indication. Supplement Approval, NDA 22387/s-017 (Mar. 31, 2021). In July 2023, Liquidia—fully aware of FDA's Bundling Rule—decided to amend the YUTREPIA 505(b)(2) NDA instead of submitting a new 505(b)(2) NDA to add the PH-ILD indication. In that amendment, Liquidia certified to the Orange Book patent information for TYVASO, and UTC timely sued Liquidia for patent infringement, but the subsequent litigation on the patents covering the new indication—the '793 patent, and U.S. Patent No. 11,826,327 ("the '327 patent")—did not trigger a 30-month stay because those patents were added to the Orange Book for TYVASO after the January 20, 2020 submission of the original YUTREPIA 505(b)(2) NDA. According to the Liquidia Letter, the amendment contained no additional data.

FDA assigned the July 2023 amendment a goal date of January 2024—6 months after submission. In January 2024, however, FDA notified Liquidia that it was not going to issue an action letter in time to meet the . . . PDUFA goal date of January 24, 2024." Liquidia Ltr. at 10.

II. LIQUIDIA'S AMENDMENT MUST BE WITHDRAWN

Liquidia misleadingly suggests that UTC is manipulating the regulatory process to thwart competition, but the real issue here is that Liquidia failed to comply with longstanding, repeatedly applied, and recently reaffirmed FDA requirements (and FDA erred in failing to apply them). FDA's Bundling Rule is clear: a new NDA must be submitted to add a new indication to a pending NDA. Liquidia's attempts to circumvent those requirements by framing FDA's longstanding Bundling Rule as a "recommendation"

[redacted]

Liquidia cannot be rewarded for its duplicity with acceptance of that amendment as of July 2023. To be consistent with its rulemakings, its policies, congressional intent, and its history of enforcement as described in our earlier letter, FDA must consider Liquidia's July 2023 amendment null and void and require the company to submit a new 505(b)(2) NDA for the PH-ILD indication.

###

We look forward to hearing from FDA on this matter. To that end, FDA's failure to take prompt action consistent with the Bundling Rule, and to UTC's satisfaction, will leave UTC with no other option than to initiate litigation against FDA.

Respectfully submitted,

Kurt R. Karst
Michael D. Shumsky
Sara W. Koblitz
Counsel for United Therapeutics Corporation

[redacted]

EXHIBIT 6

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

UNITED THERAPEUTICS CORPORATION,	)	
Plaintiff,	)	
v.	)	C.A. No. 20-755 (RGA) (JLH)
LIQUIDIA TECHNOLOGIES, INC.,	)	**REDACTED – PUBLIC VERSION**
Defendant.	)	

BRIEF IN OPPOSITION TO DEFENDANT'S MOTION SEEKING LEAVE TO MOVE FOR SUMMARY JUDGMENT OF INVALIDITY OF THE '066 AND '901 PATENTS FOR COLLATERAL ESTOPPEL AND OF INVALIDITY OF THE '901 PATENT

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I. INTRODUCTION

Liquidia's proposal to file a motion for partial summary judgment is impractical, prejudicial, and only serves to increase the burden on the Court rather than provide an efficient means of resolving this action. This Hatch-Waxman patent infringement case involves three asserted patents. The '066 and '901 patents relate to pharmaceutical compositions, pharmaceutical batches, and the related manufacturing processes. The '793 patent relates to a method of treatment for patients suffering from pulmonary hypertension. Because the parties agreed to a highly accelerated schedule, trial is set to occur only a couple months after the close of expert discovery. Even if the Court were to grant leave to file Liquidia's proposed partial summary judgment motion, review the briefing, and then grant summary judgment, the Court would still have to hold a trial in this case encompassing all three patents because Liquidia's motion would not include '066 patent, claim 8; '901 patent, claim 6; or '793 patent, claims 1, 4, or 6-8. Additionally, Liquidia's motion is substantively flawed. It grossly overreaches by attempting to procedurally short-circuit UTC's validity defenses and replace this Court's judgment with the views from a different forum involving different patents, different issues, and different evidence under a different standard of proof. Liquidia's motion should be denied.

II. STATUS OF THE PROCEEDINGS

Liquidia filed its motion for leave on November 2nd, in the middle of expert discovery and less than five months from trial. Opening expert reports were served on October 15, 2021. Scheduling Order (D.I. 20) at Exhibit A. Rebuttal expert reports were served November 12, 2021. *Id.* Reply expert reports are due December 10, 2021, and the deadline for completion of expert discovery is January 14, 2021. *Id.* The joint proposed final pretrial order is due February 28, 2022, the pretrial conference is scheduled for March 4, 2022, and the trial is slated to begin on March 28, 2022. *Id.* At the same time, due to the accelerated schedule set for this case, there also remains

outstanding fact discovery, including depositions of LGM Pharma, LLC and named inventors, as well as discovery of documents from parties and third parties.

On October 8, 2021, the PTAB issued its final written decision in the IPR of the '901 patent. UTC filed a motion for reconsideration on November 8, 2021, and, if necessary, plans to appeal the PTAB's decision.

III. SUMMARY OF ARGUMENT

Liquidia's proposed partial summary judgment motions will not resolve the case and would create the practical problem of briefing the summary judgment issues either prior to the close of expert discovery or on the eve of trial. This approach makes little sense for the Court or the parties. Expert discovery is not set to close until January 2022, a mere two months before trial. Liquidia's request to brief summary judgment either: (a) would have to occur before the conclusion of expert discovery, which would prevent the Court from reviewing all facts and inferences in UTC's favor; or (b) would have to occur after the conclusion of expert discovery, which would impinge on the parties' trial preparations and the trial itself. Even if the Court were to grant Liquidia's proposed partial summary judgment motion, the parties would still need to prepare fifteen experts for trial on all three patents and all asserted prior art references. Paradoxically, summary judgment briefing in this case would serve to *increase* the workload just before trial, rather than decrease it. *See* Liquidia Br. at 10 (citing *Exxon Corp. v. Nat'l Foodline Corp.*, 579 F.2d 1244, 1246 (CCPA 1978) ("The basic purpose of summary judgment procedure is one of judicial economy[.]"); *see also* Katherine Rhoades, *Do Not Pass Go, Do Not Stop for Summary Judgment: The U.S. District Court for the District of Delaware's Seemingly Disjunctive Yet Efficient Procedures in Hatch-Waxman Litigation*, 14 NW. J. TECH. & INTELL. PROP. 81 (2016) (noting summary judgment is uncommon in Hatch-Waxman litigation in this district).

Beyond the practical challenges the Court and the parties would face in litigating the

validity of nine patent claims on an incomplete record, Liquidia's proposed summary judgment motion is legally flawed and rests on disputed issues of material fact. First, Liquidia erroneously asserts that collateral estoppel bars the parties from litigating hotly contested issues of material fact that have never previously been considered in *any* forum. Specifically, in adjudicating the validity of the '393 patent claims, the PTAB did not resolve, much less consider, the validity of the claims in the '066 and '901 patents. The patents-in-suit have distinct claims giving rise to evidence, issues, and arguments not previously considered by the PTAB. The '066 and '901 patents claims are "presumed valid independently," 35 U.S.C. §282, and Liquidia bears the burden of demonstrating otherwise by clear and convincing evidence. *Cuozzo Speed Techs, LLC v. Lee*, 136 S.Ct. 2131, 2144 (2016) ("[I]n district court, a challenger must prove invalidity by 'clear and convincing evidence.'"); *Invitrogen Corp. v. Biocrest Mfg.*, 424 F.3d 1374, 1378 (Fed. Cir. 2005) ("That standard of proof also applies in the summary judgment context."). The burden of proof in the IPR proceeding, by contrast, is merely a preponderance of the evidence. *Cuozzo Speed Techs*136 S.Ct. at 2144. Liquidia cannot wave away the distinct factual issues in this case on a unique evidentiary record merely by relying on the PTAB's ruling in a different case involving different patent claims assessed according to a different standard of proof.

With trial set for March, the Court will soon consider the issues, patents, factual and expert testimony, and prior art references in this case. Liquidia has failed to establish good cause to seek partial summary judgment before the parties have completed all discovery, and which will not obviate the need for a trial in any event. Accordingly, UTC respectfully requests that the Court deny Liquidia's motion for leave to file partial summary judgment motions.

IV. FACTUAL BACKGROUND

On March 30, 2020 Liquidia petitioned the PTAB for IPR of the '066 patent. *Liquidia Technologies, Inc. v. United Therapeutics Corp.*, IPR2020-00769 (P.T.A.B. Mar. 30, 2020). After

considering the papers and the Moriarty and Phares prior art references Liquidia relied upon, the PTAB declined to institute IPR on any claim because it determined that Liquidia had "not established a reasonable likelihood that it would prevail in showing that at least one of the challenged claims [was] unpatentable." *Liquidia Technologies, Inc. v. United Therapeutics Corp.*, IPR2020-00769, Paper 7, at 16 (P.T.A.B. Oct. 13, 2020), attached hereto as Ex. 1.

In this case, the parties have exchanged opening and rebuttal expert reports that confirm the existence of disputed issues of material fact related to the validity of the claims at issue in Liquidia's proposed motions. Dr. Winkler has provided an expert report on behalf of Liquidia opining that the '066 and '901 patents are invalid. And Dr. Fawzi, an expert retained by UTC in this case, has offered an expert report in response expressing the opinion that the patents are valid. *Compare* Winkler Op. Rep. at ¶ 115 ("Because the '393 patent was found invalid due to its claimed product not being novel over the prior art, it is my opinion that the product-by-process claims of the '066 and '901 patents, claiming the same product, are also invalid."), *with* Fawzi Reb. Rep. at ¶ 12 ("I conclude that the claimed pharmaceutical products and pharmaceutical batches of the '066 and '901 patents do not comprise the same products as claimed in the '393 patent, and therefore the asserted claims of the '066 and '901 patents are not invalid in view of the '393 patent because they have different limitations than the '393 patent."). As Dr Fawzi stated, "I disagree with the analyses and conclusions in Dr. Winkler's report." Fawzi Reb. Rep. at ¶ 11. For example, the '393 patent claims on which Dr. Winkler's product-by-process opinion relies do not contain limitations relating to impurities. '393 Patent, claim 1; Winkler Exp. Rep. at ¶ 88, Section VII. The claims of the '066 and '901 patents, by contrast do. '066 Patent at 17:54-63; '901 Patent at 17:24-31. While Dr. Fawzi identifies these factual distinctions, Dr. Winkler does not. *See* Fawzi Reb. Rep. at ¶ 12. Dr. Fawzi notes that there are structural differences, such as the quantity and

characterization of impurities, between the pharmaceutical products and batches made according to the '066 and '901 patents and the products made according to the prior art process. *Id.* at ¶ 13. Dr. Winkler disagrees. Dr. Fawzi also notes his factual disagreements with Dr. Winkler. For example, he concludes that "Phares does not contain a working synthesis of (+)-treprostinil, or even a working synthesis of (–)-treprostinil, the enantiomer whose synthetic description Dr. Winkler relies upon." *Id.* at ¶ 14. As another example, Dr. Fawzi opines that "Dr. Winkler does not point to any reference to show that a POSA would have been concerned with the 'white needle' problem posited by Dr. Winkler, and Phares provides no indication that its diethanolamine salts would actually solve the 'white needle' problem." *Id.* at ¶ 15.

Another expert, Dr. Mody, offered a report on secondary considerations of nonobviousness for the '066 and '901 patents. Specifically, Dr. Mody opined on commercial success, long felt but unmet need, and industry praise, as well as their nexus to the '066 and '901 patents. Dr. Mody states that it was her opinion that Tyvaso had demonstrated commercial success and satisfied a long felt but unmet need for an oral inhalation solution in the treatment of pulmonary hypertension. Mody Com. Success Rep. ¶46. While none of the reports offered by Liquidia addressed secondary considerations, Liquidia's experts may address those issues in their reply reports due on December 10, 2021. And in any event, those experts reserved their rights to rebut such statements, which indicates their future intention to do so and the likelihood for additional disputes of material fact. *Id.* at ¶ 4.

V. ARGUMENT

Liquidia's motion for leave to file a motion for partial summary judgment should be denied. Motion practice at this stage of the case is impractical and would waste the parties' and the Court's resources. Even if that were not the case, partial summary judgment is not warranted here due to the highly factual inquiries at the center of Liquidia's proposed motions. And, as discussed in

Section V.B. below, Liquidia's arguments for collateral estoppel seek to impermissibly short-circuit UTC's opportunity to fully and fairly litigate these issues for the first time.

A. Liquidia's Proposed Motion for Partial Summary Judgment Would Unnecessarily Waste Resources

Briefing a motion for partial summary judgment would waste the parties' resources and work against judicial economy.

First, summary judgment briefing is unworkable under the current case schedule. The parties are currently in the middle of expert discovery which will close at the earliest on January 14, 2022, after the completion of about 16 expert depositions. If partial summary judgment motions were filed only a week later, on January 21, 2022, which would be a compressed schedule, the responsive brief under standard motion practice would be due February 4, 2022 and any reply might then be filed at the earliest a week later, on Feb. 11, 2022. At that point there would be only 17 days before the joint proposed final pre-trial order is filed for the Court to fully consider and rule on the partial summary judgment motions. It makes little sense for the parties to brief important summary judgment motions in only three weeks. But even if briefing were completed in that short time, the Court would have almost no time to rule on the motions, and any rulings by the Court would not promote efficiency for the parties, which would already have committed substantial resources preparing for trial. *See e.g.*, *Remediation Constructors, Inc. v. United States*, 68 Fed. Cl. 162, 166 (2005) (denying summary judgment on Sept. 30, 2005, because "the fact that a trial [was] scheduled to commence on October 24, 2005, a piecemeal approach to resolving this action is not an efficient use of judicial resources.").

Briefing summary judgment motions earlier is not an option, either. As mentioned, there are about 15 experts to be deposed by mid-January, rendering earlier briefing impractical. Moreover, *fact* discovery is still ongoing in this case, which may reveal additional information

relevant to the validity of the challenged claims. Because ongoing fact and expert discovery has confirmed the existence of disputed facts, it would be inefficient to engage in summary judgment motion practice prior to the close of expert discovery. *See e.g.*, *Boyer v. Taylor*, C.A. No. 06-694-GMS, 2012 WL 1132786, at *5 (D. Del. Mar. 30, 2012)(denying a motion for summary judgment because "there [were] many issues pending in [the] case and it [was] far from clear that discovery [was] complete" and because "the plaintiffs' summary judgment motion present[ed] the type of piecemeal adjudication disfavored by federal courts.").

Second, the proposed partial summary judgment motion would be a waste of time because, even if the motion were granted, the rulings would not obviate the need for a trial or even narrow the issues to be tried. Any ruling on Liquidia's proposed partial summary judgment motion would not remove any patent from the case. Instead, the trial would still need to proceed on '901 patent, claim 6 and '066 patent, claim 8, which would not be included in Liquidia's proposed motions, and all claims of the '793 patent. Unless Liquidia withdraws its validity challenges to those asserted claims, the Court would still have to assess the validity of all three patents, even if the Court were to rule in Liquidia's favor on summary judgment. Thus, engaging in summary judgment practice at this point would ultimately waste judicial resources due to the repetitive nature of the arguments that would be presented at trial were Liquidia to prevail on summary judgment. *See Pure Gold, Inc. v. Syntex (U.S.A.), Inc.*, 739 F.2d 624, 626 (Fed. Cir. 1984) ("The basic purpose of summary judgment procedure is one of judicial economy—to save the time and expense of a full trial when it is unnecessary because the essential facts necessary to decision of the issue can be adequately developed by less costly procedures, as contemplated by the FRCP rules here involved, with a net benefit to society.") (citation omitted). Summary judgment practice would only needlessly take up the Court's time and focus but will not eliminate any patents or any

prior art from being presented at trial. *See e.g.*, *Taylor v. Rederi A/S Volo*, 374 F.2d 545, 549 (3rd Cir. 1967) ("The trial court may exercise its discretion in denying summary judgment where a part of an action may be ripe for summary judgment but it is intertwined with another claim that must be tried.") (citation omitted); *Neology, Inc. v. Fed. Signal Corp.*, C.A. No. 11-672-LPS-MPT, 2012 WL 4342070, at *2 (D. Del. Sept. 21, 2012) (denying leave to file motion for summary judgment where "[t]he more efficient approach is to allow the case to proceed in accordance with the scheduling order, which was carefully negotiated between the parties").

B. Genuine Disputes of Material Fact Regarding Validity of the '066 and '901 Patents Preclude Summary Judgment

Summary judgment under Fed. R. Civ. P. 56 is also inappropriate here due to the genuine disputes of material fact. The relevant question under Rule 56 is not whether the movant is ultimately right or wrong, but whether, when viewing all facts and reasonable inferences in favor of the nonmovant, there is a genuine dispute of material fact precluding partial summary judgment. *See Scott v. Harris*, 550 U.S. 372, 380 (2007); *Wishkin v. Potter*, 476 F.3d 180, 184 (3d Cir. 2007). The validity of the asserted patent claims here involve factual disputes subject to ongoing expert discovery. Consequently, this is not a dispute amenable to resolution on summary judgment.

1. Collateral Estoppel Does Not Apply To The '066 And '901 Patents

Liquidia first argues that collateral estoppel applies to prevent UTC from asserting the '066 and '901 patents are valid. Collateral estoppel only bars a party from relitigating an issue that it had a full and fair opportunity to litigate in a previous action. *TQ Delta, LLC v. 2Wire Inc*, No. 13-1835-RGA, 2021 WL 2671296, at *3-4 (D. Del. June 29, 2021) (citing *Montana v. United States*, 440 U.S. 147, 153 (1979). In the context of patent litigation, collateral estoppel can reach "unadjudicated claims where it was shown that the adjudicated and unadjudicated claims presented *identical* issues." *Id.* (emphasis added) (quoting *Bourns, Inc. v. United States*, 537 F.2d 486, 492

(Ct. Cl. 1979)). If the issue resolved in the prior litigation is not the same issue presented in the later case, then collateral estoppel does not apply. Put differently, "collateral estoppel" applies only if the same issue has already been fully and fairly litigated by the party to be estopped. *See Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1135 (Fed. Cir. 1985) (collateral estoppel could not be applied to summary judgment for invalidity when the patent claims were subsequently changed by reissue and the reissue claims were unadjudicated in the first action, yet asserted in the second action). Liquidia bears the burden of demonstrating that the issues in the previous and current actions are identical. *See Applied Materials, Inc. v. Gemini Research Corp.*, 835 F.2d 279, 281 (Fed. Cir. 1987) (vacating a summary judgment applying collateral estoppel to a finding that claims from a continuation application did not materially differ from the rejected claims of a prior application due to district court err in failing to account for the presumption of validity).

Liquidia cannot meet that burden.

Liquidia cannot show that the issues in the '393 IPR and the current litigation are identical. As an initial matter, the claims of the '393 patent are not identical to those in the '066 and '901 patents. Indeed, although the PTAB found the claims of the '393 patent unpatentable, the PTAB denied institution of the '066 patent—finding none of the claims unpatentable—and the PTAB's recent Final Written Decision ("FWD") regarding the '901 patent did not find all claims of that patent unpatentable, either. Thus, the very PTAB decisions on which Liquidia relies demonstrate there are different issues involved in the '393, '066, and '901 patent claims.

The claim language of the patents also shows how the issues to be litigated are different and not identical, as the case law requires. For example, the PTAB's Final Written Decision on the '393 patent found that the claimed "product" in the '393 patent did not require a "particular impurity profile that is conferred by the recited process steps." FWD at 11. Thus, the claimed

"product" in the '393 patent is distinct from the "pharmaceutical composition" claimed in the '066 patent or the "pharmaceutical batch" claimed in the '901 patent, which do have claim limitations relating to the present impurities. *See, e.g.*, '066 patent, claim 1 ("a starting batch of treprostinil having one or more impurities resulting from prior alkylation and hydrolysis steps"); '901 patent, claim 1 ("A pharmaceutical batch consisting of Treprostinil or a salt thereof and impurities resulting from (a) alkylating a benzindene triol, (b) hydrolyzing the product of step (a)…"). Differences in process steps, which in the '066 and '901 patents explicitly recite relative "impurities," were not considered in the IPR adjudicating the '393 patent. *See, e.g.*, '393 FWD at 19 (stating "'product' is defined by the limitations recited in the challenged claims."); *id.* at 30 ("the record is devoid of any evidence affirmatively suggesting the existence of any structural or functional difference between treprostinil made according to Phares and that made according to the '393 patent.").

The way the PTAB and experts interpret the claims also demonstrates the '393 and '066 and '901 patents present non-identical issues. When comparing the claimed "product" of the '393 patent to the prior art, the Board found that "the *process steps* recited in the *challenged claims* [of the '393 patent] do not impart structural or functional differences to the claimed product[.]" '393 FWD at 29 (emphasis added). By contrast, Dr. Fawzi considered the scope of the '066 and '901 patents' claims, which explicitly include impurity limitations, and the process steps of the challenged claims, and concluded that the process steps *do* impart structural or functional differences. *See e.g.* Fawzi Reb. Rep. at ¶ 12 ("The scope of the '066 and '901 patent claims differ in an important way from those of the '393 patent by reciting additional limitations, including those relating to impurities. These claim limitations, absent from the '393 patent, capture at least structural and functional differences in the products…").

The *Ohio Willow Wood* case cited by Liquidia is not controlling here, as that case dealt with simple claims where there was no real dispute that the prior art (which had been found to invalidate a related patent) would similarly render obvious the asserted patent claim despite trivial differences in claim language. *See* D.I. 225 (Liquidia Br.) at 6-7, 8 (citing *Ohio Willow Wood Co. v. Alps South LLC*, 735 F.3d 1333, 1336 (Fed. Cir. 2013)). In *Ohio Willow Wood*, the court considered the application of collateral estoppel where the patent claim at issue was directed to, in essence, a sock with a gel lining used for cushioning residual stumps of amputated limbs to minimize discomfort associated with using a prosthetic. In *ex parte* reexamination proceedings, the patentee was allowed to amend the claims (overcoming prior art) to clarify that the gel coating was only on the interior of the claimed gel liners and excluded any liners with fabric that allowed gel to bleed through to the exterior surface. *Ohio Willow Wood Co.*, 735 F.3d at 1337-1338. While the litigation was stayed pending reexaminations, another district court found a related (continuation) patent invalid as obvious in view of prior art, finding that it would have been obvious to a person of ordinary skill in the art ("POSA") to select an impermeable fabric such that gel would not bleed through. *Id*. at 1341. Upon lifting the stay after reexaminations, the district court found there was collateral estoppel based on the other court's obviousness finding because the two claims used slightly different language to describe substantially the same simple invention of a sock with an interior gel liner, and the patent-holder was unable to articulate how any claim limitations were "patentably significant in view of the obvious determination regarding the claims of the [prior litigated] patent." *Id*. at 1343 (stating that the party had "not provided *any* explanation regarding [how]" the limitations changed invalidity analysis) (emphasis added); *cf. TQ Delta*, 2021 WL 2671296 at *5-6 (finding an explanation from an expert on the changed scope of asserted

claims and change in motivation to combine was sufficiently more than "mere use of different words" and changed the invalidity analysis).

Unlike *Ohio Willow Wood*, the differences in claim language between the previously litigated '393 patent and the now asserted '066 and '901 patents are material to the question of validity. For example, for the '393 patent, the Board "observe[d] that the challenged claims contain no limitations relating to the impurity profile of the recited product, 'and it is the claims ultimately that define the invention.'" '393 FWD at 18 (citing *Purdue Pharma L.P. v. Endo Pharm. Inc.*, 438 F.3d 1123, 1136 (Fed. Cir. 2006)). Because the unique claimed process steps in the '066 and '901 patents confer structural and functional distinctions to the claimed inventions over the prior art, the "issues" litigated are distinct and collateral estoppel does not apply. In fact, Liquidia implicitly recognizes that what was claimed in the '393 patent is distinct from what is claimed in the '066 and '901 patents but asserts that those differences should simply be overlooked. *See* D.I. 225 at 8. Dr. Fawzi's opinions, and the opinions of other experts in this case, demonstrate that there are disputes of material fact regarding whether prior art encompasses '066 and '901 patents' claims and whether a POSA would have a reason to combine the prior art with a reasonable expectation of success at reaching the inventions claimed by the '066 and '901 patents. Indeed, when the PTAB denied Liquidia's petition for *inter partes* review of the '066 patent, it considered the same prior art in light of the '066 claims, finding in part that reference Phares "does not suggest 'a level of one or more impurities found in the starting batch of treprostinil is lower in the pharmaceutical composition,' as claim 1 requires." Ex. 1 at 13.

Liquidia also argues that "Dr. Batra is UTC's Rule 30(b)(6) witness on Rule 30(b)(6) Topic Nos. 5-8 and 16 of identifying any differences between the '393 patent and the '901 and '066 patents." D.I. 225 at 3, citing Ex. 4 at 10-12; *see also* D.I. 225 at 5. This is simply wrong. Dr.

Batra was *not* UTC's 30(b)(6) witness on "identifying any differences between the '393 patent and the '901 and '066 patents" because UTC did not agree to present a corporate witness on that subject, as it called for expert and contention testimony. *See* Ex. 2 (UTC's written responses and objections to Liquidia's Rule 30(b)(6) notice), D.I. 178 (Liquidia letter brief regarding Liquidia's 30(b)(6) topics), D. I. 181 (UTC responsive letter brief regarding Liquidia's 30(b)(6) topics); *see also* Ex. 3 (Sept. 22 Mot. Hr'g Tr.) at 32:22-36:24 (arguments and ruling regarding scope of corporate testimony on Liquidia's 30(b)(6) topic nos. 5-8).[1] Liquidia is apparently attempting to not only mischaracterize Dr. Batra's testimony as supporting Liquidia's substantive conclusions (which it does not) but to further imply that Dr. Batra's testimony somehow limits UTC's positions (which it does not) on the mixed question of law and fact regarding the scope of claim language across different patents.

As Liquidia points out, it petitioned the PTAB to institute an IPR for the '066 patent as well. Br. At 7. The PTAB rejected Liquidia's petition after having considered arguments similar to those presented here. *See* D.I. 225 at 7 ("UTC may argue that…the PTAB did not institute Liquidia's IPR petition of the '066 patent"); *see also* Ex. 1. Liquidia's argument that "collateral

[1] Liquidia fails to point out in its statement of facts that Dr. Batra was not a 30(b)(6) witness designated for the full scope of topics 5-8, and 16. The Parties briefed this issue as a discovery dispute before Magistrate Judge Hall. As UTC and the Court have stated, portions of those topics call for expert discovery, not fact testimony from an inventor. With respect to topic nos. 5-8, the Court stated, "I agree with UTC that it need not provide testimony on the additional information that Liquidia is seeking." 9/22/21 H'rg Tr. at 33:8-11. Liquidia's topic 16 was likewise limited by UTC's objections: "UTC will provide one or more witnesses to testify concerning how UTC has synthesized treprostinil API." As the Court noted, on topics 5-8, and as Liquidia understood on topic 16, those matters were seeking expert testimony. To the extent Liquidia relies on Dr. Tuladhar's statements regarding the content of the patents, Dr. Tuladhar was not a 30(b)(6) witness and admitted to not carefully reviewing the patents prior to his deposition. Tuladhar Dep. Tr. at 8:11-19, 110:3-5. Similarly, Liquidia's statement that Dr. Tuladhar admitted that the products claimed by the '066 and '901 patents are identical to the product claimed by the '393 patent is also erroneous as such testimony requires an understanding of patent law, claim scope, and a careful analysis of the products manufactured by claimed inventions—none of which Dr. Tuladhar fully considered in his capacity as a 30(b)(1) witness.

estoppel is not a basis for an IPR petition" and therefore "that the PTAB did not instate the '066 patent IPR has no bearing on the separate legal issue of collateral estoppel" (D.I. 225 at 8) makes little sense. Had Liquidia established a reasonable likelihood that the '066 was obvious for the same reason the '393 was—i.e., the underlying rationale behind the collateral estoppel doctrine—the Board would have instituted IPR proceedings. But it did not. As the Board appreciated, the '393 patent claims are distinct from those of the '066 patent, and accordingly it embarked on a fresh and divergent analysis of the prior art and its import with respect to validity of the '066 patent's claims. Ex. 1 at 12-16. The PTAB's refusal to institute the IPR proceedings on the '066 demonstrates that it did not think Liquidia's arguments sufficiently meritorious to institute review.

Notably, Liquidia faced a lower burden in establishing invalidity in front of the PTAB than it faces here. In short, the PTAB would have instituted IPR if the PTAB believed that Liquidia had presented a reasonable likelihood that either: (1) the claims of the '066 patent suffer from the same invalidity concerns as those presented in the '393 patent; or (2) the prior art rendered the subject matter of the '066 patent invalid for anticipation or obviousness (regardless of the '393 IPR). The PTAB's rejection of the petition demonstrates that Liquidia did not meet even this *lower* threshold. Liquidia is simply wrong that the same "issue" of the validity of the '066 patent's asserted claims' scope was already decided by the '393 patent's Final Written Decision. Summary judgment based on collateral estoppel is inappropriate and briefing those issues would be a waste of time and resources.

2. <u>There Are Genuine Disputes Of Material Fact As To Validity Of The '901 Patent</u>

Contrary to Liquidia's assertions, there are several disputed issues of material fact relating to the alleged invalidity of the '901 patent. The parties' experts dispute several factual issues, demonstrating that genuine issues of material fact exist and precluding summary judgment. Rather

than grapple with the myriad disputed facts at issue, Liquidia's motion for leave attempts to gloss over those disputes by relying on the PTAB's '901 IPR Final Written Decision and pretending that that decision has automatic effect here. It does not. UTC has already sought rehearing and intends to appeal if necessary, and the PTAB's decision has certainly not been affirmed by the Federal Circuit. Moreover, Liquidia does not allege collateral estoppel based the PTAB's '901 Final Written Decision. *See* D.I. 225 at 10 ("this requested summary judgment motion is not based on collateral estoppel."). Nor could it. Only *if* the Federal Circuit affirms the PTAB's decision would it have any collateral effect in this litigation. As a result, Liquidia's heavy reliance on the PTAB's decision here is misplaced.

This Court's obviousness determination turns on "underlying factual inquires" including "(1) the scope and content of the prior art; (2) the level of ordinary skill in the prior art; (3) the differences between the claimed invention and the prior art; and (4) objective evidence of nonobviousness." *Green Edge Enterprises, LLC v. Rubber Mulch Etc.*, 620 F.3d 1287, 1298 (Fed. Cir. 2010) (affirming denial of summary judgment of invalidity for obviousness due to factual disputes regarding the *Graham* factors). For example, it is well settled that "[w]hat a reference teaches and whether it teaches toward or away from the claimed invention are questions of fact." *Par Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1196-97 (Fed. Cir. 2014).

The record has not been sufficiently developed to address all of the *Graham* factors. Expert discovery is ongoing, with both parties' experts opining on the scope and content of the prior art, whether a POSA would have a motivation to combine the asserted references, and whether a POSA would have a reasonable expectation of success in doing so. Indeed, the depth of the experts' disputes is likely to increase once reply reports are served and the experts provide their deposition testimony in this case. *See, e.g., Cipla Ltd. v. Sunovion Pharm. Inc.*, No. 15-424-LPS, D.I. 301

(D. Del. Aug. 14, 2017) ("The Court is not persuaded that the invalidity issues identified by Defendant are amenable to summary judgment before the parties even have an opportunity to take expert discovery.") (Ex. 5).

Liquidia's assertion that "UTC's evidence related to the issue of obviousness would be the same" (D.I. 225) is baseless. Liquidia simply ignores the fact that UTC has independent experts opining on the underlying facts concerning obviousness, including the assertion of the '901 patent's commercial success. *See, e.g., Continental Can Co. USA, Inc. v. Monsanto Co.*, 948 F.2d 1264, 1274 (Fed. Cir. 1991) (vacating summary judgment of invalidity for obviousness because disputed fact issues existed regarding secondary considerations, including commercial success). Liquidia's argument also relies on UTC's initial response to Liquidia's Interrogatory No. 1. But, consistent with the parties' agreement, UTC supplemented that response on September 28, 2021. *See* Ex. 4 at 7-28 (UTC's first supplemental response to Interrogatory No. 1). Liquidia's Interrogatory No. 1 sought UTC's response to Liquidia's invalidity contentions, which Liquidia supplemented the same day that UTC served its supplemental response to Interrogatory No. 1. (*See* Ex. 4). Because this September 28, 2021 exchange of supplemental disclosures marked the end of the parties' prior-agreed supplementations, there is no support for Liquidia's argument that UTC's *initial* (not even supplemental) response to Interrogatory No. 1 encapsulated the full scope of UTC's *responsive* validity positions. And in any event, UTC's responsive expert reports were served on November 12, 2021, which included UTC's experts' opinions responsive to Liquidia's obviousness opinions served October 15, 2021. UTC intends to rely on those experts' opinions and additional material at trial in this matter.

Liquidia asserts that the Court should ignore the fact that it faces a different—and *higher*—standard of proof than it did before the PTAB. In Liquidia's words, "UTC had every incentive to

persuade the PTAB of the validity of the '901 patent but failed to do so, and thus even under a clear and convincing evidence standard, UTC's evidence related to the issue of obviousness would be the same." D.I. 225 at 10. This argument borders on frivolous. In essence, Liquidia is asserting that whenever a party meets a "preponderance of the evidence" standard, it should also be deemed to meet a "clear and convincing evidence" standard because it had "every incentive to persuade" the relevant decision-maker. It is unsurprising that Liquidia cites not a single authority for this rule, because none exists. And in any event, UTC believes that the PTAB's ruling on the '901 IPR is incorrect, and sought Panel Rehearing on November 8, 2021. To the degree that rehearing request is unsuccessful, UTC intends to appeal the PTAB's Final Written Decision. *See Liquidia Techs., Inc. v. United Therapeutics Corp.*, IPR2020-00770, Paper No. 46 (Nov. 8, 2021); Liquidia Br. at 9-10, n. 8. Liquidia's argument is simply a brazen attempt to improperly flip the burden of proof to the patent holder and obfuscate the fact that Liquidia is statutorily estopped from asserting the same invalidity grounds here as those it "raised or reasonably could have raised" in the IPR proceedings. *See* 35 U.S.C. § 315(e)(2); *see also* D.I. 222 (UTC's letter brief regarding estoppel of Liquidia's '901 invalidity arguments under 35 U.S.C. § 315(e)(2)).

VI. CONCLUSION

For the foregoing reasons, UTC respectfully requests that the court deny Liquidia's Motion Seeking Leave to Move for Summary Judgment of Invalidity of the '066 and '901 Patents for Collateral Estoppel and of Invalidity of the '901 Patent (D.I. 224, 225).

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CERTIFICATE OF SERVICE

I hereby certify that on November 23, 2021, I caused the foregoing to be electronically filed with the Clerk of the Court using CM/ECF, which will send notification of such filing to all registered participants.

I further certify that I caused copies of the foregoing document to be served on November 23, 2021, upon the following in the manner indicated:

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EXHIBIT 7

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

FUNDAMENTAL INNOVATION SYSTEMS INTERNATIONAL LLC, Plaintiff, v. LENOVO (UNITED STATES), INC.; LENOVO HOLDING COMPANY INC.; LENOVO GROUP LTD., and MOTOROLA MOBILITY LLC, Defendants.	C.A. No. 20-551-CFC JURY TRIAL DEMANDED

MEMORANDUM ORDER

The parties in this patent case have jointly requested "leave to present an early summary judgment motion to the Court." D.I. 64 at 1. The parties say that resolution of the legal issue they wish to present in the motion "will clarify the scope of damages potentially at issue in the case and further the parties' settlement discussions." D.I. 64 at 1.

As a general rule, I do not allow for an early summary judgment motion unless the resolution of the motion would be case dispositive and the party seeking to file the motion agrees that it cannot file any other summary judgment motions. In light of my case load, which approaches 600 civil cases (including 300 patent cases), and based on my own experiences as a judge and the experiences of other judges who sit and have sat on this Court, I have determined that without these two

conditions early summary judgment motion practice is not an efficient use of my time and efforts. I see no reason to depart from my general rule here.

The parties also state in their letter that "[i]f the Court would prefer, the parties [will] consent to the motion being referred to Magistrate Judge Burke for a report and recommendation, pursuant to 28 U.S.C. § 636(b)(1)(B) and Fed. R. Civ. P. 72(b)." D.I. 64 at 1. But I neither prefer nor need the parties to consent to the referral of a summary judgment motion to a magistrate judge for a report and recommendation. Referrals of matters to a magistrate judge pursuant to § 636(b)(1)(B) do not require the parties' consent. And the sad reality in patent cases filed in this district is that a referral of a summary judgment motion pursuant to § 636(b)(1)(B) inevitably results in objections to the magistrate judge's report and recommendation, which the district court judge must review de novo. Such a referral therefore ends up doubling the amount of judicial resources needed to resolve the summary judgment motion in question. For that reason, I no longer make § 636(b)(1)(B) referrals of summary judgment motions in patent cases to a magistrate judge.

The parties' consent is required for referrals of motions to a magistrate judge pursuant to § 636(c). Under that section, a magistrate judge "may conduct any or all proceedings in a jury or nonjury civil matter and order the entry of judgment in

the case, when specially designated to exercise such jurisdiction by the district court . . . ." Appeals of judgments entered by a magistrate judge pursuant to § 636(c) go directly to the Court of Appeals, and referrals of matters pursuant to § 636(c) therefore conserve this Court's limited and overtaxed resources.

If the parties wish to consent to a referral pursuant to § 636(c) of the summary judgment motion they wish to present, I will make the referral. I will not, however, agree to a referral that requires both a magistrate judge and a district court judge to expend time and effort addressing the merits of a summary judgment motion.

NOW THEREFORE, at Wilmington on this Twenty-third day of November in 2021, the parties' joint request for leave to present an early summary judgment motion (D.I. 64) is DENIED.

Chief Judge

EXHIBIT 8

Viguie, Mary

From: ded_nefreply@ded.uscourts.gov
Sent: Tuesday, December 14, 2021 12:37 PM
To: ded_ecf@ded.uscourts.gov
Subject: Activity in Case 1:20-cv-00755-RGA-JLH United Therapeutics Corporation v. Liquidia Technologies, Inc. Oral Order

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U.S. District Court

District of Delaware

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Case Name: United Therapeutics Corporation v. Liquidia Technologies, Inc.
Case Number: 1:20-cv-00755-RGA-JLH
Filer:
Document Number: 267(No document attached)

Docket Text:
ORAL ORDER: Liquidias Motion for Leave to Move for Summary Judgment (D.I. [224]) is GRANTED-IN-PART and DENIED-IN-PART. The Court grants Liquidia leave to move for summary judgment of invalidity of the 066 patent and 901 patent due to collateral estoppel and denies leave to move for summary judgment of invalidity of the 901 patent as obvious. Liquidias motion and brief are due on January 7, 2022. Ordered by Judge Richard G. Andrews on 12/14/2021. (nms)

1:20-cv-00755-RGA-JLH Notice has been electronically mailed to:

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EXHIBIT 9

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

LEO PHARMA A/S, LEO LABORATORIES LIMITED, AND LEO PHARMA, INC.,	)	
Plaintiffs,	)	
v.	)	C.A. No. 16-430-JFB-SRF
PERRIGO UK FINCO LIMITED PARTNERSHIP and PERRIGO COMPANY,	)	PUBLIC VERSION
Defendants.	)	

MEMORANDUM ORDER

At Wilmington this **13th** day of **September, 2018**, the court having considered the parties' letter submissions regarding the request for leave to file a motion for summary judgment of no inequitable conduct and no derivation filed by plaintiffs LEO Pharma A/S, LEO Laboratories Limited, and LEO Pharma, Inc. (collectively, "LEO") in the above-captioned matter (D.I. 352; D.I. 364), IT IS HEREBY ORDERED THAT the request for leave to file a motion for summary judgment is DENIED for the reasons set forth below.

1. **Background.** On June 10, 2016, LEO filed the present Hatch-Waxman suit claiming that Perrigo's Abbreviated New Drug Application ("ANDA") Nos. 209018 and 209019 infringe eleven of LEO's patents[1] (the "patents-in-suit") listed in the Orange Book in connection with the drug Picato®. (D.I. 1 at ¶¶ 1, 13) The Picato® products are gels containing ingenol mebutate as the active pharmaceutical ingredient ("API") at dosage strengths of 0.015% and

[1] The original complaint identifies U.S. Patent Nos. 6,432,452 ("the '452 patent), 6,787,161 ("the '161 patent"), 6,844,013 ("the '013 patent"), 7,410,656 ("the '656 patent"), 8,278,292 ("the '292 patent"), 8,372,827 ("the '827 patent"), 8,372,828 ("the '828 patent"), 8,377,919 ("the '919 patent"), 8,536,163 ("the '163 patent"), 8,716,271 ("the '271 patent"), and 8,735,375 ("the '375 patent").

0.05%. (D.I. 73 at ¶ 1) LEO Pharma is the holder of New Drug Application ("NDA") No. 202833 for ingenol mebutate gel at concentrations of 0.015% and 0.05%, which was approved by the FDA on January 23, 2012. (*Id.* at ¶ 13) LEO's Picato® products are approved for the topical treatment of actinic keratosis. (*Id.* at ¶ 16)

2. Perrigo produced the relevant ANDAs to LEO on October 26, 2016, which indicated that they were submitted in reliance on a Drug Master File ("DMF") for the active pharmaceutical ingredient ("API") ingenol mebutate, which [redacted]

3. On May 24, 2017, LEO filed a motion to amend its complaint that added two counts for declaratory judgment of infringement of U.S. Patent Nos. 8,901,356 ("the '356 patent") and 9,416,084 ("the '084 patent")[2] which cover methods of synthesizing ingenol mebutate. (D.I. 45, Ex. 1 at ¶¶ 260-87) On June 14, 2017, in conjunction with the filing of its reply brief, LEO sought to substitute its proposed amended complaint with a revised version of the amended complaint, replacing the count directed to the '356 patent with a count directed to U.S. Patent No. 9,676,698 ("the '698 patent").[3] (D.I. 54, Ex. 1 at ¶¶ 260-87) The court issued a Memorandum Opinion and Order granting the motion to amend the complaint on September 20, 2017. (D.I. 97; D.I. 98) Perrigo answered the amended complaint on October 4, 2017. (D.I. 108)

4. Following the addition of the Process Patents, Perrigo began third-party discovery of [redacted], which revealed a preexisting

[2] LEO's motion also withdrew two counts from its original complaint related to infringement of the '452 patent. (D.I. 45, Ex. 2 at 12-16)

[3] The '698 patent issued to LEO on June 13, 2017. (D.I. 55, Ex. A) The '698 patent, together with the '084 patent, are identified as the "Process Patents" throughout this decision.

relationship between [redacted] and LEO since 2009. (D.I. 178, Ex. 1 at Exs. A & B) This discovery suggested that [redacted] with LEO, thereby disclosing its [redacted]. (*Id.* at Exs. E-F) Perrigo contends that this information was not disclosed to the United States Patent and Trademark Office ("USPTO") during prosecution of the Process Patents, raising issues of improper inventorship, unenforceability, and inequitable conduct. Consequently, Perrigo amended its affirmative defenses and counterclaims in accordance with the court's April 2, 2018 Memorandum Opinion and Order. (D.I. 244; D.I. 245)

5. On July 19, 2018, the court entered an amended scheduling order to establish discovery deadlines for Perrigo's inequitable conduct counterclaims. (D.I. 336) Fact discovery on the inequitable conduct and § 102(f) issues closed on July 27, 2018. Expert discovery on the inequitable conduct and § 102(f) issues closed on September 5, 2018. (*Id.*) A bench trial is scheduled to go forward on October 9, 2018. (4/9/18 Oral Order)

6. **Analysis.** LEO's request for leave to file a motion for summary judgment of no inequitable conduct and no derivation is denied. The original scheduling order states that, "[a]bsent an order of the Court, no summary judgment motions may be filed." (D.I. 19 at ¶ 7(b)(1)) Trial is set to begin in less than a month, which would leave less than a week between completion of briefing and the commencement of trial under the standard briefing schedule set forth in the Local Rules. *See* D. Del. LR 7.1.2(b). This does not allow sufficient time for the court to consider the merits of the proposed motion for summary judgment prior to trial. Because this matter is scheduled for a bench trial, issues pertaining to the viability of Perrigo's inequitable conduct and § 102(f) counterclaims will be presented to the trial judge for resolution, whether by way of a motion practice as appropriate under the Federal Rules of Civil Procedure,

or through the presentation of evidence at trial. Given the procedural posture of the case at this time, proceeding to trial on Perrigo's counterclaims represents the more expeditious approach.

7. The substance of the parties' dispute centers on whether there is evidence in the record demonstrating that the Process Patent inventors and/or two non-inventor employees of LEO made a false oath to the USPTO by not disclosing the alleged receipt of confidential information from [redacted] (D.I. 352 at 3; D.I. 364 at 3-4) Without reaching the merits of LEO's proposed motion for summary judgment, which is attached as Exhibit A to LEO's pending motion for leave to file, the court notes that Perrigo's response to LEO's motion for leave does not cite to any evidence in support of its contention that the [redacted] However, given the timing concerns discussed at ¶ 6, *supra*, the court concludes that Perrigo's counterclaims are properly resolved during the course of the bench trial, and will not likely result in an undue waste of resources given the scant evidence supporting the counterclaims that has been cited for the limited purpose of letter briefing the instant motion.[4]

8. **Conclusion.** In view of the foregoing analysis, LEO's request for leave to file a motion for summary judgment of no inequitable conduct and no derivation is denied.

9. Given that the court has relied upon material that technically remains under seal, the court is releasing this Memorandum Order under seal, pending review by the parties. In the unlikely event that the parties believe that certain material in this Memorandum Order should be redacted, the parties should jointly submit a proposed redacted version by no later than

[4] This case has been streamlined by stipulations to infringement of certain claims in the patents-in-suit. (D.I. 260; D.I. 343)

September 19, 2018. The court will subsequently issue a publicly available version of its Memorandum Order.

10. This Memorandum Order is filed pursuant to 28 U.S.C. § 636(b)(1)(A), Fed. R. Civ. P. 72(a), and D. Del. LR 72.1(a)(2). The parties may serve and file specific written objections within fourteen (14) days after being served with a copy of this Memorandum Order. Fed. R. Civ. P. 72(a). The objections and responses to the objections are limited to ten (10) pages each.

11. The parties are directed to the court's Standing Order For Objections Filed Under Fed. R. Civ. P. 72, dated October 9, 2013, a copy of which is available on the court's website, www.ded.uscourts.gov.

Sherry R. Fallon
United States Magistrate Judge

EXHIBIT 10

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

LIQUIDIA TECHNOLOGIES, Inc.,
Petitioner,

v.

UNITED THERAPEUTICS CORPORATION,
Patent Owner.

IPR2021-00406
U.S. Patent No. 10,716,793

PATENT OWNER RESPONSE

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wherein the powder comprises particles less than 5 micrometers in diameter.	"LIQ861 particles are a precise, uniform size (1μm) and trefoil pollen-like shape." Roscigno, Poster presentation at the Pulmonary Vascular Research Institute (PVRI) 12th Annual World Congress, Jan. 2018. Available online here.

C. Long-Felt Unmet Need

The claimed invention of the '793 patent satisfies a long-felt unmet need in the treatment of pulmonary hypertension. *See, e.g., Proctor & Gamble Co. v. Teva Pharmaceuticals USA, Inc.,* 566 F.3d 989, 998 (Fed. Cir. 2009) ("Secondary considerations of non-obviousness include . . . [the claimed invention's] satisfaction of a long-felt need."). *First*, inhaled treprostinil is indicated for a broader range of pulmonary hypertension patients than the therapeutics available at the time. *Second,* even for the treatment of pulmonary arterial hypertension, many patients found the existing therapies either intolerable or ineffective.

Inhaled treprostinil is currently approved for pulmonary arterial hypertension and pulmonary hypertension associated with interstitial lung disease. *Compare* EX2034 (2021 Tyvaso® label) *with* EX1018. The '793 patent further suggests that inhaled treprostinil in doses of 15 to 90 micrograms may also be effective for other types of pulmonary hypertension. *See, e.g.,* EX1001, 9:44-50 (explaining that the study described in example 1 included patients with idiopathic PAH, PAH other,

chronic thromboembolic pulmonary hypertension (CTEPH) and pulmonary fibrosis).

As of May 2006 – in fact, even as of January 28, 2021 – no therapies were approved for the treatment of pulmonary hypertension in patients with interstitial lung disease. EX2060, 325. As Petitioner's own expert acknowledged, there is "a completely unmet medical need" where "[t]here [is] nothing that these patients were getting as a therapy for their problems." EX2056, 105:6-8 (discussing the unmet need provided by Pulmozyme).

Even where other therapies had been approved, for example, for the treatment of pulmonary arterial hypertension, there still existed a need for the inhaled dosing regimen described in the claims of the '793 patent. By Petitioner's own admission, the claimed invention of the '793 patent satisfies a long-felt unmet need. EX2089, F-7. In promoting its own product, LIQ861 – which infringes and is an embodiment of the claimed invention, Petitioner touts that the claimed invention as embodied by LIQ861 satisfies a long-felt unmet need. EX2085. ("Given the comparable treprostinil bioavailability and similar safety profiles of LIQ861 and Tyvaso®, LIQ861 fulfills a significant unmet need for PAH patients by maximizing the therapeutic benefits of treprostinil by safely delivering doses to the lungs in 1 to 2 breaths using a discreet, convenient, easy-to-use inhaler").

CERTIFICATE OF SERVICE

The undersigned hereby certifies that a copy of the foregoing Patent Owner Response and accompanying Exhibits was served on counsel of record for Petitioner on November 10, 2021 by delivering a copy via email to the counsel of record for the Petitioner at the following addresses:

zLiquidiaIPR@cooley.com
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emilch@cooley.com
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ssukduang@cooley.com

Date November 10, 2021
FOLEY & LARDNER LLP
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Washington Harbour
Washington, DC 20007
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By /Stephen B. Maebius/
Stephen B. Maebius
Registration No. 35,264

EXHIBIT 11

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

LIQUIDIA TECHNOLOGIES, Inc.,
Petitioner,

v.

UNITED THERAPEUTICS CORPORATION,
Patent Owner.

IPR2021-00406
U.S. Patent No. 10,716,793

DECLARATION OF AARON WAXMAN, M.D., PH.D

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91. Thus, in my opinion, the combination of '212 patent, Voswinckel JESC and a POSA's general knowledge, individually or together, fail to disclose or suggest every limitation of the '793 patent claims and therefore do not render obvious claims 1-8 of the '793 patent. Further, a POSA would not be motivated to combine these references or have a reasonable expectation of success in doing so.

VI. OBJECTIVE INDICIA OF NON-OBVIOUSNESS

92. In my opinion, several objective factors also establish the non-obviousness of claims 1-8 of the '793 patent.

93. The claimed invention of the '793 patent satisfies a long-felt unmet need in the treatment of pulmonary hypertension.

94. As of the priority date, many patients found existing therapies for the treatment of pulmonary arterial hypertension to be intolerable or ineffective. As a practicing clinician, when Tyvaso® (which I understand is a commercial embodiment of the '793 patent) was approved, and as of and before the priority date, Tyvaso® was a significant advance over other available treatments for pulmonary hypertension because it did not and does not need to be administered as frequently, leading to better patient compliance. Intravenous administration involves the use of needles, chronic indwelling central venous catheters (Hickman Catheter), and complicated drug administration procedures, which patients do not prefer, and subcutaneous administration also can involve pain and includes the risk of infection.

An inhaled solution only four times per day was much safer and easier for the patient, avoiding the risks and complexities of a central venous catheter and chronic infusion pump.

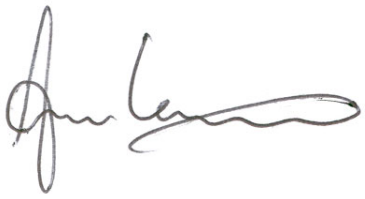
95. Inhaled treprostinil is also approved to treat a broader range of pulmonary hypertension patients than the therapeutics available at the time of the invention. *See, e.g.,* EX1001 at 9:44-50 (explaining that the study described in example 1 included patients with idiopathic PAH, PAH other, chronic thromboembolic pulmonary hypertension (CTEPH) and pulmonary fibrosis); see also EX2034 (Tyvaso® label) as compared to EX1018 (Remodulin® label) (inhaled treprostinil is currently approved for pulmonary arterial hypertension and pulmonary hypertension associated with interstitial lung disease).

96. At the time of the claimed invention and even as of today, there are no other therapies approved for the treatment of pulmonary hypertension in patients with interstitial lung disease. EX2060, Waxman *et al.,* 2021, *Inhaled Treprostinil in Pulmonary Hypertension Due to Interstitial Lung Disease*, N. Eng. J. Med. 384:325-334. I note that Petitioner's expert agrees with me that there is "a completely unmet medical need" where "[t]here [is] nothing that these patients were getting as a therapy for their problems." EX2056 (Gonda Dep. Tr.) at 105:6-8.

97. Petitioner has also acknowledged that an inhaled dosing regimen for the treatment of pulmonary arterial hypertension as described in the claims of the

I hereby declare that all statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Respectfully submitted,



Date: November 10, 2021

Aaron B. Waxman, M.D., Ph.D.

EXHIBIT 12

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TYVASO safely and effectively. See full prescribing information for TYVASO.

TYVASO® (treprostinil) inhalation solution, for oral inhalation use
Initial U.S. Approval: 2002

---------- RECENT MAJOR CHANGES ----------
Indications and Usage (1.2) 03/2021

---------- INDICATIONS AND USAGE ----------
Tyvaso is a prostacyclin mimetic indicated for the treatment of:
- Pulmonary arterial hypertension (PAH; WHO Group 1) to improve exercise ability. Studies establishing effectiveness predominately included patients with NYHA Functional Class III symptoms and etiologies of idiopathic or heritable PAH (56%) or PAH associated with connective tissue diseases (33%). (1.1)
- Pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3) to improve exercise ability. The study establishing effectiveness predominately included patients with etiologies of idiopathic interstitial pneumonia (IIP) (45%) inclusive of idiopathic pulmonary fibrosis (IPF), combined pulmonary fibrosis and emphysema (CPFE) (25%), and WHO Group 3 connective tissue disease (22%). (1.2)

---------- DOSAGE AND ADMINISTRATION ----------
- Use only with the Tyvaso Inhalation System. (2.1)
- Administer undiluted, as supplied. A single breath of Tyvaso delivers approximately 6 mcg of treprostinil. (2.1)
- Administer in 4 separate treatment sessions each day approximately 4 hours apart, during waking hours. (2.1)
- Initial dosage: 3 breaths (18 mcg) per treatment session. If 3 breaths are not tolerated, reduce to 1 or 2 breaths. (2.1)
- Dosage should be increased by an additional 3 breaths per treatment session at approximately 1- to 2-week intervals, if tolerated. (2.1)
- Titrate to target maintenance doses of 9 to 12 breaths per treatment session, 4 times daily. (2.1)

---------- DOSAGE FORMS AND STRENGTHS ----------
Sterile solution for oral inhalation: 2.9 mL ampule containing 1.74 mg treprostinil (0.6 mg per mL). (3)

---------- CONTRAINDICATIONS ----------
None. (4)

---------- WARNINGS AND PRECAUTIONS ----------
- Tyvaso may cause symptomatic hypotension. (5.1)
- Tyvaso inhibits platelet aggregation and increases the risk of bleeding. (5.2)
- Tyvaso dosage adjustments may be necessary if inhibitors or inducers of CYP2C8 are added or withdrawn. (5.3, 7.3)

---------- ADVERSE REACTIONS ----------
Most common adverse reactions (≥4%) are cough, headache, nausea, dizziness, flushing, throat irritation, pharyngolaryngeal pain, diarrhea, and syncope. (6)

To report SUSPECTED ADVERSE REACTIONS, contact United Therapeutics Corp. at 1-866-458-6479 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 03/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Pulmonary Arterial Hypertension

Tyvaso is indicated for the treatment of pulmonary arterial hypertension (PAH; WHO Group 1) to improve exercise ability. Studies establishing effectiveness predominately included patients with NYHA Functional Class III symptoms and etiologies of idiopathic or heritable PAH (56%) or PAH associated with connective tissue diseases (33%).

The effects diminish over the minimum recommended dosing interval of 4 hours; treatment timing can be adjusted for planned activities.

While there are long-term data on use of treprostinil by other routes of administration, nearly all controlled clinical experience with inhaled treprostinil has been on a background of bosentan (an endothelin receptor antagonist) or sildenafil (a phosphodiesterase type 5 inhibitor). The controlled clinical experience was limited to 12 weeks in duration *[see Clinical Studies (14)]*.

1.2 Pulmonary Hypertension Associated with ILD

Tyvaso is indicated for the treatment of pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3) to improve exercise ability. The study establishing effectiveness predominately included patients with etiologies of idiopathic interstitial pneumonia (IIP) (45%) inclusive of idiopathic pulmonary fibrosis (IPF), combined pulmonary fibrosis and emphysema (CPFE) (25%), and WHO Group 3 connective tissue disease (22%) *[see Clinical Studies (14)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Usual Dosage in Adults

Tyvaso is intended for oral inhalation using the Tyvaso Inhalation System, which consists of an ultrasonic, pulsed delivery device and its accessories.

Tyvaso is dosed in 4 separate, equally spaced treatment sessions per day, during waking hours. Each treatment session will take 2 to 3 minutes. The treatment sessions should be approximately 4 hours apart.

Initial Dosage:

Therapy should begin with 3 breaths of Tyvaso (18 mcg of treprostinil) per treatment session 4 times daily. If 3 breaths are not tolerated, reduce to 1 or 2 breaths and subsequently increase to 3 breaths, as tolerated.

Maintenance Dosage:

Dosage should be increased by an additional 3 breaths per treatment session, 4 times daily at approximately 1- to 2-week intervals. Studies establishing effectiveness in patients with PAH and PH-ILD have used target doses of 9 to 12 breaths per treatment session, 4 times daily. If adverse effects preclude titration to target dose, Tyvaso should be continued at the highest tolerated dose.

EXHIBIT 13

IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

UNITED THERAPEUTICS,)
)
Plaintiff,)
) C.A. No. 23-975-RGA
v.)
)
LIQUIDIA TECHNOLOGIES,)
)
Defendant.)

J. Caleb Boggs Courthouse
844 North King Street
Wilmington, Delaware

Tuesday, April 23, 2024
3:00 p.m.
Oral Argument

BEFORE: THE HONORABLE RICHARD G. ANDREWS, U.S.D.C.J.

APPEARANCES:

MORRIS NICHOLS ARSHT & TUNNELL LLP
BY: MICHAEL J. FLYNN, ESQUIRE

-and-

McDERMOTT WILL & EMERY LLP
BY: DOUGLAS CARSTEN, ESQUIRE
BY: ADAM BURROWBRIDGE, ESQUIRE
BY: ART DYKHUIS, ESQUIRE
BY: WILLIAM JACKSON, ESQUIRE
BY: KATHERINE CHENG, ESQUIRE
BY: ERIC ROMEO, ESQUIRE

For the Plaintiff

03:29:19 MR. CARSTEN: Sure.

03:29:19 THE COURT: -- do you agree with the general principle that if you said, you know, the first patent is I claim a method that has steps A, B and C and it cures cancer. And then later on, you learn from a clinical trial that it also prevents heart attacks. And you then say, Okay, I claim A, B, C and D, and it prevents heart attacks.

That's preempted by the first one, isn't it, because the fact that it prevents heart attacks, that actually is just a product of science or scientific relationships. And so if you claim the exact same method, but having, I don't know, different impact in the second one, the first one anticipates the second one; right?

MR. CARSTEN: I don't agree with that, Your Honor. So the cases require -- anticipation cases. It's a little bit of a mess. And they've cited their cases. We've cited ours.

But, for example, there are two *Glaxo* cases. One of which, *Glaxo vs. Kali*, the claimed method was treating nausea. And the prior art method was treating migraine sufferers, and there was no inherent anticipation there.

So I'm presuming that in your hypothetical that the prior patent didn't say anything about heart attacks; right?

THE COURT: Right.

MR. CARSTEN: That's exactly the situation we have here. So *Glaxo vs. Kali*, no inherent anticipation there.

Glaxo vs. Teva, treating nausea and vomiting was the claimed method. The prior art method was treating migraine pain.

Now, again, two different indications, and the Court there said, "Look, not all of these patients are going to be suffering from nausea because of their migraines; and therefore, it's a different patient class." So a different patient class can get out of anticipation.

We have that here. We have the '793 patent which is dedicated to hemodynamic benefits. That's within that vessel, the vessels between the heart and the lung I talked about earlier.

Here, we have pulmonary hypertension associated with ILD interstitial lung disease. So it's not just pulmonary hypertension and or with. It's pulmonary hypertension associated with interstitial lung disease. That's a subset. We have a genus and a species.

And a species, when there's surprising results, can be patentable over a broader genus. That's black letter patent law, Your Honor. And so that's exactly what we have here, Your Honor.

Moreover, Your Honor, in addition to that distinction, you have differences in dosing. The '793 patent talked about one to three breaths. The '327 patent does not have a breath restriction in terms of limiting it to one to three.

THE COURT: But one breath -- well, go ahead.

MR. CARSTEN: And the '793 patent, as you recall, Your Honor, had this claim term of single event dose. So you were doing a single event dose to administer.

And there was testimony in that prior case about how each one of those single event doses is going to give the therapeutic effect there. I.e., that hemodynamic, the changes in the vasculature that change the pressure.

We're not talking about any of that in connection with the '327. We're talking about improving exercise capacity, which is a functional measure.

THE COURT: I take it you think improving exercise capacity is a limitation here?

MR. CARSTEN: Yes, Your Honor. Certainly for today, we're assuming that as well. We'll see what arguments Liquidia comes up with in the future. But for purposes of today, we can assume it is.

And so, as a result, then, Your Honor, we fall squarely within the line of cases that suggests that a different patient population or a different indication. For

example, *Rapoport vs. Dement*, another case we cited. The claimed method was treating sleep apnea. The prior art method was treating anxiety, which is a common symptom resulting from sleep apnea. Again, patentable.

And so we fall within that line of cases where the difference in the patient population and or the difference in the indication, that resulting indication. And we have both here between the '327 and the '793. Render the claim to be patentable.

So I don't agree with Your Honor that -- with your hypothetical that you'd actually be anticipated in that circumstance.

THE COURT: Okay. So one of the things that was discussed in the briefing that I could use a little more explanation on was the idea that -- well, actually as a prelude to this, is it the case that unless you're successful in some other forum, as far as you're concerned, if there was a preliminary injunction against the ILD indication, that would have no impact on whether or not Liquidia can launch for the PAH indication?

MR. CARSTEN: That's right, Your Honor. This case is solely about the launch on the ILD indication.

I believe you heard my learned friend, Mr. Sukduang, talk about some communications with the FDA. That's all news to us. But as far as we know, the pending

04:33:18 MR. CARSTEN: I think from there, my friend
04:33:26 switched over to validity, and he started out with
04:33:38 anticipation. I'm going to show you Slide 12 from our deck,
04:33:42 Your Honor.
04:33:43 The '793 patent simply doesn't anticipate. I
04:33:49 can read these bullets, but there is nothing in the '793
04:33:54 patent whatsoever about exercise capacity, period, full
04:33:58 stop. The words just don't even appear in there.
04:34:01 THE COURT: So why didn't you assert this
04:34:02 against this -- against in the new case?
04:34:07 MR. CARSTEN: In the new case, exercise capacity
04:34:10 is -- oh, why did we assert it? Because administration of
04:34:14 Treprostinil will have the hemodynamic changes that were
04:34:19 claimed within the '793 patent. And those hemodynamic
04:34:23 changes are covered by the '793 patent.
04:34:26 THE COURT: Right.
04:34:26 MR. CARSTEN: And so --
04:34:27 THE COURT: All right.
04:34:28 MR. CARSTEN: Go ahead, Your Honor. You can
04:34:32 skin the cat --
04:34:32 THE COURT: The '793 patent and the hemodynamic
04:34:35 changes, they were covered in the last case.
04:34:37 MR. CARSTEN: They were for pulmonary arterial
04:34:40 hypertension treatments, Your Honor. Right. This was --
04:34:42 this case -- that case was about, based upon Your Honor's

claim construction, the only indication that Liquidia was pursuing at the time was PAH.

THE COURT: Right.

MR. CARSTEN: And remember PAH is the constrictions of that vasculature. The thinned tube, the narrow tubes that causes it --

THE COURT: Right. But I guess my understanding is that in this case, the one we're having a preliminary injunction about, which was against the ILD indication, that you asserted the '973 (sic) patent.

MR. CARSTEN: The '793 patent.

THE COURT: '793 patent.

MR. CARSTEN: We did, along with other patents, Your Honor. Yes.

THE COURT: Right, right. But, I mean, presumably you thought the '793 patent covered this indication; right?

MR. CARSTEN: Well, it is relevant to the indication. That's what we told the FDA. We told the Patent Office.

THE COURT: But, I mean, when you file a suit with a patent, you don't file it because it's irrelevant. You file it because you say it's infringed.

MR. CARSTEN: Exactly. And by administration of the Treprostinil to these patients suffering from ILD, you

will do two things. You will increase or you will reduce the pressure in that vasculature as it works for treating pulmonary arterial hypertension. And you will also increase exercise capacity.

As Your Honor pointed out, you can skin -- you know, you can skin the cat. Sorry with all the cat metaphors here, Judge. That seems odd. But you can skin the cat in terms of different approaches and different effects of a particular approval or a particular method of treatment, right.

The method of treatment might be administering Treprostinil to treat pulmonary hypertension. And recall, Judge, your construction in the previous case for pulmonary hypertension included all pulmonary hypertension, including these Group 3 PH-ILD patients.

And so we felt and still feel that we had a sufficient and robust case on '793. The only reason that the withdrawal of -- the '793 was withdrawn was because of the PTAB, which we will be filing a cert petition, and you know, hope springs eternal.

THE COURT: You're an optimist.

MR. CARSTEN: I am an optimist, Judge. But having said that, there is no specificity in the '793 patent about targeting these PH-ILD patients, the special class of Group 3 patients. There's nothing in there to improve their

exercise capacity.

So, again, for all the reasons I went through at the outset, Your Honor, this is a different patent that is designed and claimed in a different way. It gets to that improved hemodynamics, not the functional aspect of a subset of the PH patients that were claimed in the '793.

These patents are harmonious. They can coexist. There is no anticipation for all of these reasons.

In order to get an argument of anticipation, Your Honor, they need to rely upon things that are not prior art such as the INCREASE study. And so they turn to the INCREASE study because they can't say that hemodynamic effects are therapeutic effects, right. That's what they're trying to say, which is the opposite of what they said before.

Now, here's a couple of quotes from the opening argument and the closing argument delivered by my friend in the last case. What you'll find, generally speaking, is you'll find statements from both UTC's and Liquidia's experts in the prior case that are sort of wiggly about whether there's a relationship between therapeutic efficacy for PAH and hemodynamic capacity or hemodynamic effects.

Now, remember, PAH has to do with the vasculature. So when you administer Treprostinil and you open up those -- the vasculature, you're going to drive the

EXHIBIT 14

[redacted]

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

UNITED THERAPEUTICS CORPORATION,	)	
Plaintiff	)	C.A. No. 23-975 (RGA) (SRF)
v.	)	[redacted]
LIQUIDIA TECHNOLOGIES, INC.,	)	
Defendant.	)	

PLAINTIFF'S AMENDED FIRST SUPPLEMENTAL RESPONSES AND OBJECTIONS TO DEFENDANT'S FIRST SET OF INTERROGATORIES TO PLAINTIFF (NOS. 1-6)

Pursuant to Rules 26 and 33 of the Federal Rules of Civil Procedure, Plaintiff United Therapeutics Corporation ("UTC" or "Plaintiff"), by and through its undersigned counsel, hereby responds to Defendant Liquidia Technologies, Inc.'s ("Liquidia" or "Defendant") First Set of Interrogatories (Nos. 1–6).[1]

PRELIMINARY STATEMENT

The following responses are made solely for the purpose of, and in relation to, this action. Each response is provided subject to all appropriate objections (including, without limitation, objections relating to competency, relevancy, propriety, proportionality, and admissibility) that would require the exclusion of any statement provided herein if that statement were made by a witness testifying in court. All such objections are reserved and may be interposed at the time of trial.

[1] UTC previously offered supplemental responses to Liquidia's Interrogatory Nos. 1, 2, 3, and 6 prior to the close of fact discovery on November 13, 2024. Consistent with the Court's November 12, 2024 Memorandum Order (D.I. 193), UTC hereby serves supplemental responses to Liquidia's Interrogatory Nos. 4 and 5.

in the individual references that Liquidia relies upon. Not only do the references lack sufficient disclosure, the purported prior art identified by Liquidia is also deficient and does not establish the obviousness of the Asserted Claims because the references lack the requisite motivation to combine and fail to provide the POSA with a reasonable expectation of success. Invalidity Contentions are also silent about the fact that certain of its asserted prior art references were already considered by the patent examiner during prosecution of the '327 patent. In fact, the patent examiner already considered ***five*** of Liquidia's seven purported prior art references. Where, as here, "the examiner considered the asserted prior art and basis for the validity challenge during patent prosecution, th[e] burden [to prove invalidity by clear and convincing evidence] becomes particularly heavy." *Impax Labs.,* 545 F.3d at 1314. Liquidia has not, and cannot, meet such an exacting standard. Moreover, Liquidia's obviousness arguments are impermissibly driven by "the insidious attraction of the siren hindsight." *See W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1553 (Fed. Cir. 1983); *see also Millennium Pharms., Inc. v. Sandoz Inc.*, 862 F.3d 1356, 1367 (Fed. Cir. 2017) ("However, '[t]he inventor's own path itself never leads to a conclusion of obviousness; that is hindsight. What matters is the path that the person of ordinary skill in the art would have followed, as evidenced by the pertinent prior art.'" (quoting *Otsuka Pharm. Co., Ltd. v. Sandoz, Inc.*, 678 F.3d 1280, 1296 (Fed. Cir. 2012))).

A. <u>Liquidia fails to establish obviousness-type double patenting over the '793 patent</u>

"Double patenting is altogether a matter of what is claimed." *Gen. Foods Corp. v. Studiengesellschaft Kohle GmbH*, 972 F.2d 1272, 1277 (Fed. Cir. 1992). Indeed, "[i]t is the claims, not the specification, that define an invention . . . . And it is the claims that are compared when assessing double patenting." *Ortho Pharm. Corp. v. Smith*, 959 F.2d 936, 943 (Fed. Cir. 1992) (citing *Raytheon Co. v. Roper Corp.,* 724 F.2d 951, 957 (Fed. Cir. 1983)). The obviousness-type double patenting inquiry also requires courts to consider individual limitations in the context of

the claim as a whole. *See Gen. Foods Corp.*, 972 F.2d at 1274 ("[E]ach claim is an *entity* which must be considered *as a whole*.").

As an initial matter, Liquidia has not proven that the '793 patent is prior art, and in any event, only the claims of the '793 patent (with narrow exceptions that do not apply here) can be considered in assessing whether the claims of the '327 patent are invalid over the '793 patent due to obviousness-type double patenting. *Ortho Pharm.*, 959 F.2d at 943. Further, the claims of the '793 patent disclose less than the specification, and for anticipation Liquidia cited portions of the '793 patent specification, which belies its attempt to argue that the claims of the '793 patent alone render the '327 patent claims obvious under obvious-type double patenting. UTC also incorporates by reference the deficiencies in Liquidia's anticipation argument described above in section I.A.

Further, the '793 patent claims do not teach all of the limitations of the Asserted Claims. *See, e.g.*, § I.A., *supra*; D.I. 26, 28, 65, 96. As explained above, the '793 patent (including its claims) fails to teach "a method of improving exercise capacity in a patient having pulmonary hypertension associated with interstitial lung disease." As the parties have agreed, the claims of the '327 patent require improving exercise capacity. D.I. 94 at 4. By contrast, the claims of the '793 patent do not mention "exercise capacity" at all. *See* '793 patent at Claims 1-8. Indeed, the Court has already reasoned that "the '793 patent does not teach administering inhaled treprostinil to specifically improve exercise capacity, nor does the disclosed data discuss improved exercise capacity." D.I. 96 at 10.

The fact that the '793 claims may include hemodynamic effects in various types of PH patients does not establish obviousness of the methods of the '327 patent, which recite improving exercise capacity in patients having PH-ILD. *See Bayer Pharma AG v. Watson Labs., Inc.*, 212 F.

Supp. 3d 489, 517 (D. Del. 2016) ("It is well-settled that a narrow species can be non-obvious and patent eligible despite a patent on its genus." (quoting *Abbvie Inc. v. Mathilda & Terence Kennedy Inst. of Rheumatology Tr.*, 764 F.3d 1366, 1379 (Fed. Cir. 2014)) . As in this case, targeting a subset of patients can "reflect a new and useful invention [despite] prior art . . . disclosing the treatment method to patients generally," particularly "where the new patient subset displayed unexpected results." *Prometheus Labs., Inc. v. Roxane Labs., Inc.*, 805 F.3d 1092, 1098 (Fed. Cir. 2015). Likewise, inventions are patentably distinct where "a particular treatment may be effective with respect to one subset of patients and ineffective (and even harmful) to another subset." *Id.* Here, the '793 patent claims do not express specific preferences for treating PH-ILD. *See Pernix Ireland Pain DAC v. Alvogen Malta Operations Ltd.*, 323 F. Supp. 3d 566, 591 (D. Del. 2018); *Atofina v. Great Lakes Chem. Corp*., 441 F.3d 991, 999 (Fed. Cir. 2006). The Court here has also recognized the disclosure lacking in the '793 patent. *See* D.I. 96 at 10 ("Based on the record before me, the '793 patent does not teach administering inhaled treprostinil to specifically improve exercise capacity, nor does the disclosed data discuss improved exercise capacity. Defendant's contention that Plaintiff's own experts have equated a positive hemodynamic effect with improvements in exercise capacity is unpersuasive."). Liquidia argues that "a POSA would have understood that treating pulmonary hypertension, including PH-ILD, using inhaled treprostinil would inherently improve the exercise capacity of a patient." Invalidity Contentions at 75. That is incorrect for the reasons identified above and in Section I.A. Furthermore, as discussed below, the teachings of the prior art, including the claims of the '793 patent, would not have given the POSA a reasonable expectation of success in practicing the methods of the '327 patent. *See also infra* § I.A-H.

CERTIFICATE OF SERVICE

I hereby certify that on November 19, 2024, copies of the foregoing were caused to be served upon the following in the manner indicated:

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/s/ Michael J. Flynn

Michael J. Flynn (#5333)

EXHIBIT 15

[redacted]

U.S. FOOD & DRUG ADMINISTRATION

NDA 213005

TENTATIVE APPROVAL

Liquidia Technologies, Inc.
Attention: Jennifer Weidman, PhD, RAC
Vice President, Global Regulatory Affairs
419 Davis Dr., Suite 100
Morrisville, NC 27560

Dear Dr. Weidman:

Please refer to your new drug application (NDA) dated and received January 24, 2020, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Yutrepia (treprostinil) inhalation powder, for oral inhalation.

We acknowledge receipt of your amendment dated May 7, 2021, which constituted a complete response to our November 24, 2020, action letter.

We also acknowledge receipt of your amendment dated July 24, 2023, which constituted a resubmission to our November 4, 2021, action letter.

This NDA proposes the use of Yutrepia (treprostinil) inhalation powder for the treatment of pulmonary arterial hypertension (PAH; WHO Group I) and pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3), to improve exercise ability.

We have completed our review of this application, as amended. It is tentatively approved under 21 CFR 314.105(a); therefore, this application is not approved and will not be approved until FDA issues an approval letter after any necessary additional review of the application. Enclosed are the tentatively approved labeling (text for the Prescribing Information, Instructions for Use, and Carton and Container labeling). This tentative approval determination is based upon information available to the Agency at this time, (i.e., information in your application and the status of current good manufacturing practices of the facilities used in the manufacture and testing of the drug product). This determination is subject to change on the basis of new information that may come to our attention.

Final approval of your application is subject to expiration of a period of patent protection and/or exclusivity. Therefore, final approval of your application may not be granted before the period has expired.

To obtain final approval of this application, submit an amendment two or six months prior to the date you believe that your NDA will be eligible for final approval, as appropriate. In your cover letter, clearly identify your amendment as **"REQUEST FOR FINAL APPROVAL."** This amendment should provide the legal/regulatory basis for your request for final approval and should include a copy of any relevant court order or judgment settlement, or licensing agreement, as appropriate. In addition to a safety update, the amendment should also identify changes, if any, in the conditions under which your product was tentatively approved, i.e., updated labeling; chemistry, manufacturing, and controls data; and risk evaluation and mitigation strategy (REMS). If there are no changes, clearly state so in your cover letter. Any changes require our review before final approval and the goal date for our review will be set accordingly.

Until we issue a final approval letter, this NDA is not approved, and cannot be legally marketed and the use of the enclosed tentatively approved labeling is not permitted for marketing this drug product. If you believe that there are grounds for issuing the final approval letter before the expiration of the patent(s) and/or exclusivity protection, you should amend your application accordingly.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We note that if this application is ultimately approved, you will need to meet these requirements.

Postmarketing requirements will be renegotiated at the time you submit your request for final approval.

If you have any questions, please contact Brian Cooney, Regulatory Project Manager, at (301) 796-0886 or via email at brian.cooney@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, MD, PhD
Acting Deputy Director
Division of Cardiology and Nephrology
Office of Cardiology, Hematology, Endocrinology, and Nephrology
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURES: (tentatively approved)

- Content of Labeling
  - Prescribing Information
  - Instructions for Use
  - Carton and Container Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use YUTREPIA™ safely and effectively. See full prescribing information for YUTREPIA™.

YUTREPIA™ (treprostinil) inhalation powder, for oral inhalation
Initial U.S. Approval: 2002

----------INDICATIONS AND USAGE----------

YUTREPIA is a prostacyclin mimetic indicated for the treatment of:

- Pulmonary arterial hypertension (PAH; WHO Group 1) to improve exercise ability. Studies establishing effectiveness predominately included patients with NYHA Functional Class III symptoms and etiologies of idiopathic or heritable PAH (56%) or PAH associated with connective tissue diseases (33%). (1.1)
- Pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3) to improve exercise ability. The study establishing effectiveness predominately included patients with etiologies of idiopathic interstitial pneumonia (IIP) (45%) inclusive of idiopathic pulmonary fibrosis (IPF), combined pulmonary fibrosis and emphysema (CPFE) (25%), and WHO Group 3 connective tissue disease (22%). (1.2)

----------DOSAGE AND ADMINISTRATION----------

- For oral inhalation only. Do not swallow YUTREPIA capsules. Use only with the provided inhaler (2)
- YUTREPIA should be administered 3 to 5 times per day. The contents of each capsule can be inhaled in 2 breaths. (2.1)
- See *Dosage and Administration* for full instructions on dosing of patients who are treprostinil-naïve or transitioning from treprostinil inhalation solution to YUTREPIA (2.1)

----------DOSAGE FORMS AND STRENGTHS----------

YUTREPIA inhalation powder contained in capsule is available in 4 strengths: 26.5 mcg, 53 mcg, 79.5 mcg, 106 mcg (3)

----------CONTRAINDICATIONS----------

None (4)

----------WARNINGS AND PRECAUTIONS----------

- Treprostinil may cause symptomatic hypotension. (5.1)
- Treprostinil inhibits platelet aggregation and increases the risk of bleeding. (5.2)
- Dosage adjustments may be necessary if inhibitors or inducers of CYP2C8 are added or withdrawn. (5.3, 7.1)
- May cause bronchospasm: Patients with a history of hyperreactive airway disease may be more sensitive. (5.4)

----------ADVERSE REACTIONS----------

Most common adverse reactions with YUTREPIA (≥10%) are cough, headache, throat irritation, and dizziness. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Liquidia Technologies, Inc. at 1-XXX-XXX-XXXX or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling (Instructions for Use).

Revised: 08/2024

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Pulmonary Arterial Hypertension

YUTREPIA is indicated for the treatment of pulmonary arterial hypertension (PAH; WHO Group 1) to improve exercise ability. Studies establishing effectiveness predominately included patients with NYHA Functional Class III symptoms and etiologies of idiopathic or heritable PAH (56%) or PAH associated with connective tissue diseases (33%).

The effects diminish over the minimum recommended dosing interval of 4 hours; treatment timing can be adjusted for planned activities.

While there are long-term data on use of treprostinil by other routes of administration, nearly all controlled clinical experience with inhaled treprostinil has been on a background of bosentan (an endothelin receptor antagonist) or sildenafil (a phosphodiesterase type 5 inhibitor). The controlled clinical experience was limited to 12 weeks in duration [*see Clinical Studies (14)*].

1.2 Pulmonary Hypertension Associated with ILD

YUTREPIAis indicated for the treatment of pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3) to improve exercise ability. The study establishing effectiveness predominately included patients with etiologies of idiopathic interstitial pneumonia (IIP) (45%) inclusive of idiopathic pulmonary fibrosis (IPF), combined pulmonary fibrosis and emphysema (CPFE) (25%), and WHO Group 3 connective tissue disease (22%) [*see Clinical Studies (14.2)*].

2 DOSAGE AND ADMINISTRATION

2.1 Usual Dosage In Adults

YUTREPIA capsules are for oral inhalation only and should be used only with the supplied inhaler.

YUTREPIA Dosing in treprostinil-naïve patients:

In patients naïve to treprostinil, therapy should begin with 26.5 mcg 3 to 5 times per day, in 2 breaths based on patient response.

Dosing in patients transitioning from treprostinil inhalation solution (Tyvaso):

Patients transitioning from treprostinil inhalation solution (Tyvaso), can begin YUTREPIA therapy 3 to 5 times per day, in 2 breaths, using the doses specified below (Table 1):

Table 1: YUTREPIA Dosing in Patients Transitioning from Treprostinil Inhalation Solution

Current Tyvaso Dose*	YUTREPIA Dose
Breaths	mcg
≤5	26.5

≥6 and ≤8	53
≥9 and ≤11	79.5
≥12 and ≤14	106
≥15 and ≤17	132.5
≥18	159

*Each breath of Tyvaso delivers approximately 6 mcg of treprostinil

In treprostinil-naïve patients and those transitioning from treprostinil inhalation solution, dose increases of 26.5 mcg per dose each week may be implemented, as tolerated. The target maintenance dosage is 79.5-106 mcg, 4 times daily. Doses above 848 mcg per day have not been studied in patients with PAH.

3 DOSAGE FORMS AND STRENGTHS

YUTREPIA inhalation powder contained in capsule available in 4 strengths:

- 26.5 mcg: opaque yellow cap and clear body capsule with "LIQUIDIA 26.5" in black radial imprint on capsule cap.
- 53 mcg: opaque green cap and clear body capsule with "LIQUIDIA 53" in white radial imprint on capsule cap.
- 79.5 mcg: opaque blue cap and clear body capsule with "LIQUIDIA 79.5" in white radial imprint on capsule cap.
- 106 mcg: opaque purple cap and clear body capsule with "LIQUIDIA 106" in white radial imprint on capsule cap.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Symptomatic Hypotension

Treprostinil is a pulmonary and systemic vasodilator. In patients with low systemic arterial pressure, treatment with treprostinil may produce symptomatic hypotension.

5.2 Risk of Bleeding

Treprostinil inhibits platelet aggregation and increases the risk of bleeding.

5.3 Effect of Other Drugs on Treprostinil

Co-administration of a cytochrome P450 (CYP) 2C8 enzyme inhibitor (e.g., gemfibrozil) may increase exposure (both C_{max} and AUC) to treprostinil. Co-administration of a CYP2C8 enzyme inducer (e.g., rifampin) may decrease exposure to treprostinil. Increased exposure is likely to increase adverse events associated with treprostinil administration, whereas decreased exposure is likely to reduce clinical effectiveness *[see Drug Interactions (7.1) and Clinical Pharmacology (12.3)]*.

EXHIBIT 16

Atty. Dkt. No. 080618-2002

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Inventor Name:	Leigh Peterson
Title:	TREATMENT FOR INTERSTITIAL LUNG DISEASE
Appl. No.:	17/233061
Filing Date:	4/16/2021
Examiner:	WARD, PAUL V
Art Unit:	1624
Confirmation Number:	8404

AMENDMENT AND REPLY UNDER 37 CFR § 1.111

Mail Stop AMENDMENT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

This paper replies to the outstanding non-final Office Action mailed March 6, 2023.

Amendments to the Claims are reflected in the listing of claims that begins on page 2.

Remarks begin on page 5.

Amendments to the Claims:

This listing of claims will replace all prior versions and listings of claims in the application:

Listing of Claims:

1. (Currently Amended) A method of improving exercise capacity in a patient having ~~treating a~~ pulmonary hypertension associated with interstitial lung disease ~~due to a condition which is selected from a chronic lung disease, hypoxia and a combination thereof~~, comprising administering by inhalation to the patient having pulmonary hypertension associated with interstitial lung disease ~~a subject having the pulmonary hypertension due to the condition selected from a chronic lung disease, hypoxia and a combination thereof~~ an effective amount of at least 15 micrograms up to a maximum tolerated dose of treprostinil or a pharmaceutically acceptable salt thereof in a single administration event that comprises ~~an amount of~~ at least 6 micrograms per breath.

2-7. (Canceled)

8. (Currently Amended) The method of claim 1, wherein said administering provides a statistically significant increase of a 6 minute~~s~~ walk distance in the patient ~~subject~~ after 8 weeks, 12 weeks, or 16 weeks of the administering.

9. (Currently Amended) The method of claim 1, wherein said administering increases a 6 minute~~s~~ walk distance of the patient by at least 10 m after 8 weeks, 12 weeks, or 16 weeks of the administering.

10. (Currently Amended) The method of claim 1, wherein said administering provides a statistically significant reduction of a plasma concentration of NT-proBNP in the patient ~~subject~~ after 8 weeks, 12 weeks, or 16 weeks of the administering.

11. (Currently Amended) The method of claim 1, wherein said administering reduces a plasma concentration of NT-proBNP in the patient ~~subject~~ by at least 200 pg/ml after 8 weeks, 12 weeks, or 16 weeks of the administering.

12. (Currently Amended) The method of claim 1, wherein said administering provides a statistically significant reduction of ~~a number of~~ at least one exacerbations ~~s~~ of the interstitial lung disease ~~chronic lung disease~~.

13. (Currently Amended) The method of claim 1, wherein said administering provides a statistically significant reduction of clinical worsening events due to the interstitial lung disease ~~chronic lung disease~~.

14. (Original) The method of claim 13, wherein the clinical worsening events comprise at least one of hospitalization for cardiopulmonary indication and a decrease in a 6-minute walk distance by more than 15% compared a baseline 6-minute walk distance prior to the administering.

15. (Currently Amended) The method of claim 1, wherein said administering provides a statistically significant improves of forced vital capacity (FVC) in the patient ~~subject~~ after 8 weeks, 12, weeks or 16 weeks of the administering.

16. (Currently Amended) The method of claim 15, wherein said administering improves the forced vital capacity (FVC) in the patient ~~subject~~ by at least 20 ml after 8 weeks, 12 weeks, or 16 weeks of the administering.

17. (Canceled)

18. (Previously Presented) The method of claim 1, wherein said administering is performed by a pulsed inhalation device.

19. (Original) The method of claim 18, wherein the pulsed inhalation device contains an inhalation solution comprising treprostinil or a pharmaceutically acceptable salt thereof.

20. (Original) The method of claim 18, wherein the pulsed inhalation device is a nebulizer.

21. (Original) The method of claim 18, wherein the pulsed inhalation device is a dry powder inhaler comprising a dry powder comprising treprostinil or a pharmaceutically acceptable salt thereof.

22. (Currently Amended) The method of claim 1, wherein the effective amount of treprostinil or a pharmaceutically acceptable salt administered to the patient ~~subject~~ in a single inhalation administration event is from 15 µg to 100 µg.

23. (Currently Amended) The method of claim 22, wherein the single inhalation administration event does not exceed 15 breaths by the patient ~~subject~~.

24. (Currently Amended) The method of claim 1, wherein said administering ~~increase~~ increases a 6 minute~~s~~ walk distance of [[in]] the patient ~~subject~~ by at least 10 m after 8 weeks of the administering.

25. (Currently Amended) The method of claim 1, wherein said administering ~~increase~~ increases a 6 minute~~s~~ walk distance of [[in]] the patient ~~subject~~ by at least 15 m after 12 weeks of the administering.

26. (Currently Amended) The method of claim 1, wherein said administering ~~increase~~ increases a 6 minute~~s~~ walk distance of [[in]] the patient ~~subject~~ by at least 15 m after 16 weeks of the administering.

REMARKS

Applicant respectfully requests reconsideration and allowance of the present application.

Status of Claims

Claims 1, 8-13, 15-16 and 22-26 are currently amended, without prejudice or disclaimer, to advance the prosecution and to present the claimed subject matter in a clearer manner. Claims 2-7 are canceled. Support for the amended claims may be found throughout the specification as filed, including for amended claim 1 on pages 10, 33-34, 40 and 52 as well in original, now-canceled claim 4. No new matter is added.

After the amendment, claims 1, 8-16, and 18-26 remain pending.

Rejections Under 35 U.S.C. § 102

The Office Action contains five anticipation rejections. Specifically, claims 1-16 and 18-26 stand rejected as allegedly anticipated by each of (i) Malinin (WO2015/138423), (ii) Zhang (WO2016/205202), (iii) Morgans (WO2012/009097), (iv) Wade (WO2008/098196), and (v) Bosc (WO2016/176399). Applicant respectfully traverses each of the five rejections.

(1) Malinin

Malinin does not teach or suggest elements of claim 1:

(i) "administering by inhalation to the patient having pulmonary hypertension associated with interstitial lung disease an effective amount of at least 15 micrograms up to a maximum tolerated dose of treprostinil or a pharmaceutically acceptable salt thereof"; and

(ii) "a single administration event that comprises at least 6 micrograms per breath".

Malinin teaches nothing regarding either treprostinil doses for inhalation or an amount of treprostinil administered per breath. Thus, Malinin is not an anticipatory reference because Malinin does not teach all the elements of amended claim 1. Accordingly, Applicant requests withdrawal of the rejection.

(2) Wang

Wang does not teach or suggest several elements of claim 1:

(i) "administering by inhalation to the patient having pulmonary hypertension associated with interstitial lung disease an effective amount of at least 15 micrograms up to a maximum tolerated dose of treprostinil or a pharmaceutically acceptable salt thereof";

(ii) "a single administration event that comprises at least 6 micrograms per breath"

(iii) "improv[es] exercise capacity in a patient having pulmonary hypertension associated with interstitial lung disease."

Wang teaches nothing regarding either treprostinil doses for inhalation or an amount of treprostinil administered per breath. Furthermore, Wang teaches nothing regarding improving exercise capacity in any patient. In sum, Wang is not an anticipatory reference because Wang does not teach all the elements of amended claim 1. Accordingly, Applicant requests withdrawal of the rejection.

(3) Morgans

Morgans does not teach or suggest elements of claim 1:

(i) "administering by inhalation … treprostinil or a pharmaceutically acceptable salt thereof";

(ii) "administering by inhalation to the patient having pulmonary hypertension associated with interstitial lung disease an effective amount of at least 15 micrograms up to a maximum tolerated dose of treprostinil or a pharmaceutically acceptable salt thereof";

(iii) "a single administration event that comprises at least 6 micrograms per breath"; and

(iv) "improv[es] exercise capacity in a patient having pulmonary hypertension associated with interstitial lung disease".

Morgans teaches nothing regarding administering treprostinil by inhalation. Applicant's computerized search revealed that Morgans mentions a word staring with "inhal" only once in paragraph [0147], when Morgans states that "the mitotic kinesin inhibitor is administered intrapulmonarily by inhalation." However, treprostinil is not the mitotic kinesin inhibitor administered in Morgans by inhalation, so this statement is not relevant to the instant claims.

Because Morgans teaches nothing regarding administering treprostinil by inhalation, Morgans teaches nothing about treprostinil doses for inhalation or an amount of treprostinil administered per breath. Furthermore, Morgans teaches nothing regarding improving exercise capacity in any patient.

In sum, Morgans is not an anticipatory reference because Morgans does not teach all the elements of amended claim 1. Accordingly, Applicant requests withdrawal of the rejection.

(4) Wade

Wade does not teach or suggest "a single administration event that comprises at least 6 micrograms per breath" as amended claim 1 recites. Accordingly, Applicant requests withdrawal of the rejection.

(5) Bosc

Bosc does not teach or suggest elements of claim 1:

(i) "administering by inhalation … treprostinil or a pharmaceutically acceptable salt thereof";

(ii) "administering by inhalation to the patient having pulmonary hypertension associated with interstitial lung disease an effective amount of at least 15 micrograms up to a maximum tolerated dose of treprostinil or a pharmaceutically acceptable salt thereof";

(iii) "a single administration event that comprises at least 6 micrograms per breath"; and

(iv) "improv[es] exercise capacity in a patient having pulmonary hypertension associated with interstitial lung disease".

Bosc teaches nothing regarding administering treprostinil by inhalation. Bosc mentions treprostinil in paragraph [0009] as a second therapeutic to be used together with Bosc's retinoic acid receptor-related orphan nuclear receptor (ROR) inhibitor. However, Bosc does not teach or suggest that the second therapeutic, such as treprostinil, is administered by inhalation.

Because Bosc teaches nothing regarding administering treprostinil by inhalation, Bosc also teaches nothing about either treprostinil doses for inhalation or an amount of treprostinil administered per breath. Furthermore, Bosc teaches nothing regarding improving exercise capacity in any patient.

In sum, Bosc is not an anticipatory reference because Bosc does not teach all the elements of amended claim 1. Accordingly, Applicant requests withdrawal of the rejection.

Deficiencies of the Office Action Regarding Dependent Claims

Although the Office rejected each of the dependent claims as anticipated by each of the cited references, the Office did not provide any explanation relating to how the cited references

teach the separate limitations of the dependent claims. If the Office intends to reject any of the dependent claims in the next Office Action, Applicant requests a reasoned explanation regarding how the prior art teaches or suggests specific elements of the dependent claims, so Applicant can adequately respond.

Concluding Remarks

Applicant believes that the application is in condition for allowance. Favorable reconsideration is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance prosecution.

The Commissioner is hereby authorized to charge any additional fees which may be required for this application to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, applicant hereby petitions for such extensions under 37 CFR § 1.136 and authorizes payment of any such extension fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date May 10, 2023

By /Stephen B. Maebius/

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EXHIBIT 17

PTO/SB/08 (modified)

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet 1 of 6

Complete if Known	
Application Number	Unassigned
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First Named Inventor	Hitesh BATRA
Art Unit	Unassigned
Examiner Name	Unassigned
Attorney Docket Number	080618-1892

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Examiner Signature		Date Considered	

4829-0862-8648.1

PTO/SB/08 (modified)

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet 2 of 6

Complete if Known	
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Filing Date	Herewith
First Named Inventor	Hitesh BATRA
Art Unit	Unassigned
Examiner Name	Unassigned
Attorney Docket Number	080618-1892

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Examiner Signature		Date Considered	

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Examiner Signature		Date Considered	

4829-0862-8648.1

EXHIBIT 18

[redacted]

ADD IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

UNITED THERAPEUTICS CORPORATION, Plaintiff, v. LIQUIDIA TECHNOLOGIES, INC., Defendant.	C.A. No. 23-975 (RGA) (SRF)

EXPERT REPORT OF DR. NICHOLAS HILL

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IX. UTC FAILED TO DISCLOSE MATERIAL REFERNCES TO THE USPTO

A. UTC Was Aware of the Size of the PH-ILD Patient Population and its Commercial Value

213. PAH occurs at a rate of approximately 2-5 in 100,000 people.[221] The prevalence of diagnosed and undiagnosed PH-ILD is estimated to range between 30,000 and 70,000 people in the United States.[222] I have reviewed a slideshow and transcript of a 2018 presentation by Dr. Aaron Waxman during UTC's Science Day on the findings of a study conducted by Dr. Mariana Faria-Urbina in 2018.[223] During his 2018 Science Day presentation, Dr. Waxman, speaking to the therapeutic opportunity for inhaled treprostinil, noted that "WHO Group III includes those patients with lung diseases of a number of different backgrounds[,] but that the focus of the presentation would be "on those patients who have probably the most prevalent diseases including chronic obstructive pulmonary disease, interstitial lung disease and a mix of the 2[,]" further noting that "[w]hen we think about the prevalence, its actually a ***huge medical problem*** out there."[224]

214. During the prosecution of the '327 patent from April 16, 2021 to November 28, 2023, UTC was well aware of the size and potential commercial value of the PH-ILD market. I have also reviewed the transcript of a 2017 presentation given by Dr. Waxman in which Dr. Waxman states, referring to Group 1 PH, that efforts to treat pulmonary vascular disease had "been focused on one ***very small subset*** of pulmonary vascular disease[,]" but that when other patients

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[221] GBD 2021 Pulmonary Arterial Hypertension Collaborators, *Global, regional, and national burden of pulmonary arterial hypertension, 1990-2021: a systematic analysis for the Global Burden of Disease Study 2021*, LANCET RESPIRATORY MED. (2024) at 5. This publication will be produced concurrently with this expert report.

[222] D.I. 55 (Decl. of Doug Kidder) at 10 (citing Liquidia Corporation's Form 10-K for 2022 (UTC_PH-ILD_002744)).

[223] A. Waxman, *The iTRE Study: Therapeutic Opportunity for Inhaled Treprostinil in Patients with PH Secondary to Primary Pulmonary Vascular Disease*, UTHR Science Day 2018 (2018) ("Waxman Presentation 2018") at Slides 11-16 (LIQ_PH-ILD_00101301); LIQ_PH-ILD_00140569 at -609.

[224] *Id*. (emphasis added).

with pulmonary vascular disease are considered, there was "a large number of potential patients[,]" as the treatment that had been directed at pulmonary vascular remodeling could "potentially benefit any patient with a form of pulmonary vascular disease[,]" including those classified as Group 3.[225] Dr. Waxman also noted that "if you don't get labels of what your're looking at, you wouldn't be able to discern one patient from another with pulmonary vascular disease."[226]

215. Dr. Waxman's 2017 remarks regarding the prevalence of WHO Group 1 PH as a "very small subset" of the total number of patients with a form of pulmonary vascular disease, and 2018 presentation describing the potential to treat WHO Group 3 patients, is consistent with my understanding of the disease landscape. In my opinion, Dr. Waxman's understanding is reflective of the knowledge of practicing physicians, who by 2017 would have been aware of the size and potential market for the treatment of patients with a form of pulmonary vascular disease other than Group 1 as the pathways that are active in patients with PAH are also active in patients with Group 3[.]"[227]

216. [redacted]

[225] 2017 Waxman JVMS Presentation (LIQ_PH-ILD_00147328) at 2:2-3:22 (emphasis added).
[226] *Id*.
[227] *Id*.
[228] UTC_WAT00628950-951
[229] *Id*.
[230] *Id*. (emphasis added).

217. In 2018, during an earnings call, Dr. Rothblatt, referring to PH-ILD patients, made the following statements to investors:

> In fact, they believe that this drug works even better in that indication than in the Group I indication in terms of, at least, the exercise ability that they saw in their patients, discounting any placebo effects that might be involved. So with that kind of data, some of which has been presented in posters and maybe even publications -- I don't know, but I've definitely seen posters, we went ahead and then had the statistics to power of the study for statistical significance, the one in the ILD population and the other in the COPD population, which are 2 distinct populations.
>
> …
>
> [B]oth through the effort of our medical affairs group over the years in supporting investigator-sponsored studies and through the kindness and generosity of certain payers around the country who have gone ahead and upon the initiative of their physicians, were able to enable some WHO Group III patients to benefit [from Tyvaso and], there were unmistakable signals the some of the leading physicians in this field[,] I called out one of them on the call, Dr. Waxman, but there are many others, who said to UT, "This drug works."[231]

218. In my opinion, Dr. Rothblatt's 2015 email to Roger Jeffs regarding her communication with Dr. Tapson as well as her 2018 statements made during UTC's earnings calls, are indicative of UTC's awareness surrounding the size and commercial value of the PH-ILD market and UTC's interaction with key opinion leaders, including Dr. Waxman. UTC was not only knowledgeable regarding the efficacy of Tyvaso and efforts by physicians and payors which "enable[d] some WHO Group III patients to benefit," but UTC itself, through its medical affairs group, had supported investigator-sponsored studies.[232]

[231] UTC 2018 Earnings Call (LIQ_PH-ILD_00000001) at -010.
[232] UTC_WAT00628950-951; UTC 2018 Earnings Call (LIQ_PH-ILD_00000001) at -010

219. In 2018, Dr. Rothblatt told investors that based on reported results, Tyvaso worked even better in PH-ILD patients than in those diagnosed with PAH.[233] Dr. Rothblatt's and UTC's awareness of the size and commercial value of the market for treating PH-ILD informed its later statements to shareholders in 2022 offering "greater assurance about the doubling of revenues by the end of '25" due to the uptake of Tyvaso DPI.[234] Similarly, in 2023, Dr. Rothblatt reported that Liquidia's Yutrepia, which at the time was set to be launched only for the treatment of PAH, would not challenge UTC's projected double-digit growth, noting that "there is so much robust room for growth and improvement in pulmonary hypertension[,]" which includes PH-ILD.[235]

220. In my opinion, Dr. Rothblatt's statements demonstrate knowledge of the potential market for PH-ILD and UTC's confidence that despite another product launching for the PAH indication, UTC would meet its revenue targets driven by the additional PH-ILD indication.

221. Therefore, it is my opinion that during the prosecution of the '327 patent, UTC was well aware of the size and potential commercial value of the PH-ILD patient population, and consequently the value of the patent protection provided by the '327 patent which is directed to a method of treating PH-ILD with inhaled treprostinil.

B. Stephen Maebius, Shaun Snader, and Peter Smith Had a Duty to Disclose Information to the USPTO

222. I understand from counsel that Stephen Maebius, Shaun Snader, and Peter Smith, all owed a duty of disclosure to the USPTO, which required that they disclose information, including references, to the USPTO material to the prosecution of the '327 patent. I also understand from counsel that this duty of disclosure existed from the time of patent application filing until the '327 patent issued.

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[233] LIQ_PH-ILD_00000001 at -004-007.
[234] LIQ_PH-ILD_00000013 at -018.
[235] *Id.* at -022.

1. Stephen Maebius

223. According to his CV, Mr. Maebius is a partner at Foley & Lardner LLP with over 30 years of experience.[236] Based on Mr. Maebius' CV, it is my understanding that Mr. Maebius "helps clients protect their innovation and transact business involving intellectual property assets."[237] Mr. Maebius' CV further indicates that prior to becoming a lawyer, he was a patent examiner in the Biotechnology Group of the USPTO.[238]

224. [redacted].[239]

225. Mr. Snader's deposition transcript further shows that Mr. Maebius, was granted the "Power of Attorney to Prosecute Applications Before the USPTO" on behalf of UTC.[240]

226. Mr. Maebius also acted as lead counsel during the '793 IPR.[241] Mr, Maebius was present at an oral hearing before the PTAB for the '793 IPR during which discussions took place regarding the admissibility and relevance of evidence from the District Court proceedings concerning the '793 patent.[242]

227. Thus, it is my opinion that during the prosecution of the '793 patent, Mr. Maebius was aware of the proceedings before the PTAB ('793 IPR) and the District Court proceedings

[236] Maebius Dep., Ex. 1.
[237] *Id*.
[238] *Id*.
[239] Maebius Dep. Tr. at 24:17-19, 43:17-46:17, 52:16-53:7.
[240] Power of Attorney (UTC_PH-ILD_009419 at -524); Snader Dep. Tr. at 67:18-69:18.
[241] May 13, 2022 PTAB Oral hearing (LIQ_PH-ILD_00101524 at -526).
[242] *Id.* at -526, -528-537, -549-552, -574-575, -602; UTC Press Release, July 24, 2023 (LIQ_PH-ILD_00101321).

regarding the '793 patent as evidenced by the fact that UTC submitted documents from the District Court proceedings during the '793 IPR.[243]

2. Shaun Snader

228. According to his LinkedIn profile, Shaun Snader is Vice President and Associate General Counsel (Intellectual Property) at UTC and is responsible for managing UTC's intellectual property portfolio, including supervising patent litigation for UTC.[244] I have reviewed the deposition transcript of Mr. Snader, in which Mr. Snader confirmed that he was "primarily responsible at United Therapeutics for the supervision and management of the patent prosecution that led to the issuance of the '793 patent[.]"[245]

229. During his deposition, Mr. Snader also confirmed that he signed the "Power of Attorney to Prosecute Applications Before the USPTO" on behalf of UTC, granting Stephen Maebius the power to prosecute the '327 patent application.[246]

230. Mr. Snader also indicated that generally, he has "at least some level [of] involvement in substantive submissions" to the patent office and confirmed that it is "generally true that outside counsel would wait for [his] approval before filing a substantive response in a patent prosecution matter for United Therapeutics[.]"[247] [redacted].[248]

231. Mr. Snader further confirmed during his deposition that he was counsel of record in the '793 patent IPR, [redacted]

[243] I submitted expert reports in both the '793 patent IPR and the earlier district court litigation between UTC and Liquidia regarding the '793 patent.
[244] Snader Dep., Ex. 2.
[245] Snader Dep. Tr. at 228:19-229:13.
[246] Power of Attorney (UTC_PH-ILD_009419 at -524); Snader Dep. Tr. at 68:2-69:18.
[247] *Id*. at 40:2-44:2.
[248] Maebius Dep. Tr. at 44:1-49:15.

[redacted][249]

232. Mr. Snader also testified during his deposition that he appeared as counsel for UTC in the Federal Circuit appeal of the '793 patent District Court case and publicly commented on the '793 patent District Court opinion regarding the infringement and validity of the '793 patent, and the Federal Circuit's affirmance of this opinion regarding the '793 patent.[250]

233. It is my opinion that based on his position at UTC, his testimony during deposition describing his involvement in the '793 IPR, and his appearance in the Federal Circuit appeal of the District Court litigation concerning the '793 patent, Mr. Snader was aware of the proceedings before the PTAB, District Court, and the Federal Circuit concerning the '793 patent during the prosecution of the '327 patent.

234. [redacted]

[redacted][251]

235. It is my opinion that the February 12, 2024, letter to the FDA further evidences Mr. Snader's and UTC's knowledge of the materiality of the '793 patent for the prosecution of the '327 patent application.

[249] *Id*. at 102:21-103:4, 104:2-14, 104:22-105:15, 106:5-107:18, 140:13-141:10, 150:16-151:13.
[250] UTC Entry of Appearance, District Court Appeal (LIQ_PH-ILD_00101851); UTC Press Release August 31, 2022 (LIQ_PH-ILD_00101319); UTC Press release; July 24, 2023 (LIQ_PH-ILD_00101321).
[251] LIQ_PH-ILD_00000847; Snader Dep. Tr. 229:19-237:2.

3. Dr. Peter Smith

236. I understand, from reviewing his CV, that Dr. Peter Smith is UTC's Vice President of Product Development.[252] I also understand, from my review of the '327 patent cover page, that Dr. Smith is a named inventor of the '327 patent.

237. [redacted].[253]

238. In Dr. Waxman's letter to the FDA, Dr. Waxman stated – with Dr. Smith's knowledge and approval as demonstrated by the November 15, 2017, email – that he, Dr. Waxman, was involved in preliminary studies, utilizing inhaled treprostinil in PH-ILD patients, and based on these studies, "anticipated that patients with ILD-PH may be more likely to benefit from prostacyclin therapy such as treprostinil."[254] Dr. Waxman's letter to the FDA also referenced the INCREASE study and Agarwal 2015.[255]

239. [redacted][256]

[252] Smith Dep., Ex. 1.
[253] UTC_LIQ00104554; UTC_LIQ00104555; Smith Dep. Tr. at 185:4-186:15.
[254] UTC_LIQ00104555 at -556.
[255] *Id.*
[256] UTC_PH-ILD_081580 at -593; Smith Dep. Tr. at 157:24-159:24, 162:10-164:2.

240. [redacted][257]

241. It is my opinion that Dr. Smith, was familiar with Dr. Waxman's letter to the FDA, and the Agarwal 2015 reference during the prosecution of the '327 patent.

C. References Not Disclosed to USPTO

242. I am informed by counsel that certain references were not disclosed to the USPTO during the prosecution of the '327 patent. These references include: (1) the '793 Patent District Court Opinion, (2) my '793 Patent District Court trial testimony; (3) Federal Circuit affirmance of the '793 Patent District Court Opinion (including the Court's claim construction); (4) '793 IPR submissions. As described below, in my opinion, each of these references were material to the prosecution of the '327 patent, and therefore should have been disclosed to the USPTO during the prosecution of the '793 patent.

1. '793 Patent District Court Opinion and My Trial Testimony

243. Counsel has advised me that on June 4, 2020, before the '327 patent application was filed, UTC filed a complaint against Liquidia in the United States District Court for the District of Delaware.[258] UTC amended this complaint to further assert that Liquidia infringed its '793 patent on July 22, 2020.[259] I was an expert witness in this litigation and testified live at trial.

244. The Court's opinion in the District Court litigation includes its claim construction regarding the meaning of "pulmonary hypertension" in the '327 patent claims. The District Court

[257] Snader Dep. Tr. at 63:22-64:5.
[258] *United Therapeutics Corp. v. Liquidia Techs., Inc.*, C.A. No. 1:20-cv-755-RGA-JLH, D.I. 1 (D. Del. June 4, 2020).
[259] *United Therapeutics Corp. v. Liquidia Techs., Inc.*, C.A. No. 1:20-cv-755-RGA-JLH, D.I. 16 (D. Del. July 22, 2020).

concluded that based on the specification of the '793 patent, the scope of "treating pulmonary hypertension" in claim 1 includes "treating all five Groups of PH."[260]

245. I understand from counsel that the District Court trial concerning the '793 patent took place in March 2022 and the District Court issued its opinion in August 2022.[261] I further understand that the opinion was issued during the prosecution of the '327 patent application and prior to Mr. Maebius' amendment to the pending claims of the '327 patent covering interstitial lung disease.

246. As I mentioned, I testified during the '793 patent District Court litigation. I have reviewed the trial transcript containing my testimony where I testified regarding the meaning of "pulmonary hypertension" in the claims of the '793 patent. As I stated during trial, "'[p]ulmonary hypertension' as used, as far as I can tell in the patent, and would be used as a general term by a POSA comprises all the five different groups. It refers to . . . any condition where . . . there's an elevation of the pulmonary pressure, pulmonary pressures."[262]

247. This understanding of pulmonary hypertension is informed by column 1 line 41 of the '793 patent. As I stated during trial, "the first sentence says that pulmonary hypertension may occur due to various reasons, and the different entities of pulmonary hypertension were classified, based on clinical and pathological grounds, in five categories according to the latest WHO convention."[263]

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[260] *United Therapeutics Corp. v. Liquidia Techs., Inc.*, No. 1:20-cv-755-RGA-JLH, D.I. 433 at 38 (D. Del. Aug. 31, 2022) ("District Court Opinion"); *United Therapeutics Corp. v. Liquidia Techs., Inc.*, 624 F. Supp. 3d 436, 464 (D. Del. 2022), *aff'd*, 74 F.4th 1360 (Fed. Cir. 2023).
[261] *Id.*
[262] LIQ_PH-ILD_00101296 at -1298
[263] *Id.*

248. As I also previously testified, the pulmonary hypertension patients described in Example 1 of the '793 patent included patients in pulmonary hypertension Group 3, which includes patients with interstitial lung disease.[264]

249. It is my opinion, that given that the "treating pulmonary hypertension" term in the '793 patent claims was found to cover methods of treating all Groups of PH, including WHO Group 3 PH which includes interstitial lung disease, the proceedings before the District Court and its issued Opinion were material to the prosecution of the '327 patent claims which cover treating pulmonary hypertension associated with interstitial lung disease. Specifically, claim 1 was amended on May 10, 2023 during the prosecution of the '327 patent to read as indicated below:

> Claim 1: (Currently Amended) A method of improving exercise capacity in a patient having ~~treating a~~ pulmonary hypertension associated with interstitial lung disease ~~due to a condition which is selected from a chronic lung disease, hypoxia and a combination thereof~~, comprising administering by inhalation to the patient having pulmonary hypertension associated with interstitial lung disease ~~a subject having the pulmonary hypertension due to the condition selected from a chronic lung disease, hypoxia and a combination thereof~~ an effective amount of at least 15 micrograms up to a maximum tolerated dose of treprostinil or a pharmaceutically acceptable salt thereof in a single administration event that comprises ~~an amount of~~ at least 6 micrograms per breath.[265]

250. Additionally, it is clear that Mr. Snader also believed that the '793 patent covers the same approved indication of treating PH-ILD which is covered by at least claim 1 of the '793 patent. I have reviewed a letter from UTC submitted to the FDA on February 12, 2024, which states the following:

> During the pendency of the 30-month stay for the PAH indication, ***UTC received approval of the new PH-ILD indication***. Supplement Approval, NDA 22387/s-017 (Mar. 31, 2021). In July 2023, Liquidia—fully aware of FDA's Bundling Rule—decided to amend the YUTREPIA 505(b)(2) NDA instead of submitting a new 505(b)(2) NDA to add the PH-ILD indication. In that amendment, Liquidia certified to the Orange Book patent information for TYVASO, and UTC timely sued

[264] *Id.*
[265] '327 patent file history at UTC_PH-ILD_009739.

> Liquidia for patent infringement, but ***the subsequent litigation on the patents covering the new indication—the '793 patent, and U.S. Patent No. 11,826,327 ("the '327 patent")***—did not trigger a 30-month stay because those patents were added to the Orange Book for TYVASO after the January 20, 2020 submission of the original YUTREPIA 505(b)(2) NDA. According to the Liquidia Letter, the amendment contained no additional data.[266]

This passage makes clear that UTC, including Mr. Snader, believes that both the '327 patent ***and*** the '793 patent cover the new indication for Tyvaso, which is the indication directed to treatment of PH-ILD. Mr. Snader testified during his deposition in this case that he was involved in the preparation of this letter.[267]

251. I have been informed that the '793 patent was submitted to the USPTO during the '327 patent prosecution. [redacted].[268] I have reproduced claim 1 of the '793 patent below.

> A method of treating pulmonary hypertension comprising administering by inhalation to a human suffering from pulmonary hypertension a therapeutically effective single event dose of a formulation comprising treprostinil or a pharmaceutically acceptable salt thereof with an inhalation device, wherein the therapeutically effective single event dose comprises from 15 micrograms to 90 micrograms of treprostinil or a pharmaceutically acceptable salt thereof delivered in 1 to 3 breaths.[269]

252. I have also been informed that neither the District Court's claim construction nor my trial testimony was submitted. In my opinion, these documents were material to the prosecution of the '327 patent claims and should have been submitted because they would have made clear to the Examiner that the method of treating pulmonary hypertension in the '793 patent covers the '327 patent claimed method of improving exercise capacity in PH-ILD as recited in claim 1 as indicated below. While Mr. Snader and Mr. Maebius submitted the '793 patent during

[266] LIQ_PH-ILD_00000847 at -852 (emphasis added); *see also* Snader Dep. Tr. at 229:19-237:2.
[267] Snader Dep. Tr. at 229:19-231:9.
[268] Maebius Dep. Tr. at 87:2-13.
[269] UTC_PH-ILD_009772 at -796 (claim 1).

prosecution, the District Court's claim construction and my testimony provided valuable context as to the scope and meaning of the '793 patent claims as encompassing treating PH-ILD patients that the USPTO did not have access to. In my opinion, had the USPTO been provided the District Court's claim construction and my trial testimony, that would form the basis to render at least claim 1 of the '327 patent unpatentable based on the '793 patent alone, or in combination with prior art cited by the USPTO during prosecution. For that reason, the District Court Opinion and my District Court Trial testimony are material references, which should have been disclosed to the USPTO during the prosecution of the '327 patent.

a. Claim 1 of '327 patent: "A method of improving exercise capacity in a patient having pulmonary hypertension associated with interstitial lung disease"

253. As indicated above, the '793 patent was found to cover methods of treating all 5 PH groups. PH-ILD is a type of PH that falls within Group 3 PH and is therefore covered by the '793 patent's method of treatment. The fact that claim 1 of the '327 patent refers to a method of improving exercise capacity instead of a method of treatment, does not change my opinion. In my opinion, an improvement in exercise capacity, as reflected in for example an improvement in 6MWD, is clearly treating PH-ILD. An improvement in exercise capacity is something I routinely assess in my PH patients when determining whether a medication is effectively treating a patient. Moreover, to the extent UTC argues that the '793 patent is directed to hemodynamic changes that also does not change my opinion that the '793 patent covers the claimed method of improving exercise capacity in a patient having PH-ILD. This is because treprostinil is a vasodilator and its therapeutic effect is accomplished by favorable changes in a patient's hemodynamics. Therefore, in my experience, favorable hemodynamic changes in a PH patient generally correlate with improvements in exercise capacity.

b. Claim 1 of '327 patent: "comprising administering by inhalation to the patient having pulmonary hypertension associated with interstitial lung disease an effective amount of at least 15 micrograms up to a maximum tolerated dose of treprostinil or a pharmaceutically acceptable salt thereof in a single administration event that comprises at least 6 micrograms per breath."

254. The claimed dosing regimen of inhaled treprostinil in the '327 patent is also encompassed within the '793 patent's dosing regimen. First, claim 1 of the '793 patent recites "administering by inhalation . . . a formulation comprising treprostinil." This disclosure of the use of inhaled treprostinil in '793 patent claim 1 and elsewhere in the specification encompasses the '327 patent claim 1's requirement for administering treprostinil by inhalation. Second, claim 1 of the '793 patent recites:

> a therapeutically effective single event dose of a formulation comprising treprostinil or a pharmaceutically acceptable salt thereof with an inhalation device, wherein the therapeutically effective single event dose comprises from 15 micrograms to 90 micrograms of treprostinil or a pharmaceutically acceptable salt thereof delivered in 1 to 3 breaths.[270]

255. This dosing in the '793 patent overlaps with the '327 patent's claimed dosing. Both patents require that the effective dose of inhaled treprostinil is at least 15 micrograms provided in a single event dose. Additionally, the '327 patent requires that the single administration event comprise at least 6 micrograms per breath. This requirement is covered by the '793 patent claim's requirement that 15 micrograms can be delivered in 1 to 3 breaths. Obviously, the delivery of 15 micrograms in either 1 or 2 breaths would result in delivery of 15 or 7.5 micrograms per breath, respectively. Both of these amounts are at least 6 micrograms per breath as required by claim 1 of the '327 patent.

[270] UTC_PH-ILD_009772 at -796 (claim 1).

256. In my opinion, the '793 patent covers at least claim 1 of the '327 patent and therefore renders claim 1 of the '327 patent invalid. Accordingly, the '793 District Court Opinion on claim construction and my corresponding trial testimony were material to the prosecution of the '327 patent because they make clear, and I believe would have made clear to the '327 patent examiner, the scope of the '793 patent and that it would invalidate, alone or in combination with prior art cited during prosecution, of at least claim 1 of the '327 patent.

2. Federal Circuit Affirmance of the Claim Construction

257. I understand that on July 24, 2023, prior to the allowance of the '327 patent, the Federal Circuit affirmed the District Court's decision and agreed with me and the District Court that the '793 patent's claimed "'treating pulmonary hypertension' includes treating all five groups of pulmonary hypertension patients."[271] Neither Mr. Snader nor Mr. Maebius submitted the Federal Circuit's affirmance to the USPTO during prosecution of the '327 patent.

258. It is my opinion that both the District Court Opinion and the Federal Circuit's affirmance confirm that the claims of the '793 patent, including the mode of administration (inhalation), dosing, and number of breaths, and dose per breath, are utilized for all five PAH Groups, including patients with interstitial lung disease–the subject matter of the issued claims of the '327 patent.

259. Thus, it is my opinion that the Federal Circuit decision of July 24, 2023, which affirmed the District Court's claim construction that the '793 patent covers methods of treating all five PH Groups was material to the prosecution of the '327 patent and should have been submitted to the USPTO during the '327 patent prosecution for the same reasons provided for the '793 patent District Court opinion above.[272]

[271] *United Therapeutics Corp. v. Liquidia Tech. Inc.*, 74 F.4th 1360, 1368 (Fed. Cir. 2023).
[272] LIQ_PH-ILD_00101446.

3. '793 IPR Submissions and Federal Circuit's Invalidity Findings

260. I have reviewed UTC's Patent Owner Response, submitted in conjunction with the '793 IPR, in which UTC stated that "[t]he claimed invention of the '793 patent satisfies a long-felt unmet need in the treatment of pulmonary hypertension."[273]

261. In its Patent Owner Response, UTC further described the invention in the '793 patent, stating that "[i]nhaled treprostinil is currently approved for pulmonary arterial hypertension and pulmonary hypertension associated with interstitial lung disease[,]" and that "[a]s of May 2006 – in fact, even as of January 28, 2021 – no therapies were approved for the treatment of pulmonary hypertension in patients with interstitial lung disease."[274]

262. I have reviewed portions of the'793 IPR Declaration of UTC's expert, Dr. Aaron Waxman filed in support of UTC's Patent Owner Response, in which he stated the following in a section of his declaration directed to unmet need in support patentability of the '793 patent:

> Inhaled treprostinil is also approved to treat a broader range of pulmonary hypertension patients than the therapeutics available at the time of the invention[,]" and that "[a]t the time of the claimed invention and even as of today, there are no other therapies approved for the treatment of pulmonary hypertension in patients with interstitial lung disease.[275]

263. Both the Patent Owner Response and Dr. Waxman's supporting declaration sought to support the validity of the '793 patent by indicating that the treatment of PH-ILD covered an unmet need that was covered by the '793 patent. In my opinion, such an argument only makes sense if the claims of '793 patent include methods of treating PH-ILD – a fact which I testified to during my prior District Court testimony and which I continue to believe is true.

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[273] Patent Owner Response (LIQ_PH-ILD_00000110 at -180).
[274] *Id.* at -180-181.
[275] Waxman IPR Decl. (LIQ_PH-ILD_00102032) at ¶95-96.

264. I understand that the PTAB issued a Final Written Decision (FWD) invalidating the '793 patent on July 19, 2022, as obvious under 35 U.S.C. § 103. Thereafter, UTC filed a Notice of Appeal of the PTAB panel's FWD. On December 20, 2023, the Federal Circuit issued its opinion affirming the PTAB's decision finding the '793 patent invalid.[276]

265. I believe these references would have been material to the prosecution of the '327 patent because the arguments and opinions offered by UTC and Dr. Waxman in the POR and Waxman declaration, respectively, rely on the fact that the '793 patent claims cover methods of treating PH-ILD and specifically the FDA approved indication on the Tyvaso label. These references are therefore material to the prosecution of the '327 patent for all the same reasons discussed for the District Court Opinion above. These references provide valuable context, not only of the scope of the '793 patent claims, but also UTC's own affirmative positions that the claims of the '793 patent cover the same subject matter of the '327 patent. Thus, this information would permit the USPTO to reject the claims of the '327 patent based on the '793 patent alone or in combination with additional prior art because these statements would confirm the '793 patent's clam scope. Additionally, the PTAB's FWD is also material because it found all claims of the '793 patent invalid as obvious. Given that the '793 patent claim invalidates at least claim 1 of the '327 patent, either alone or in combination with additional prior art, in my opinion, the PTAB's finding that the '793 patent claims were obvious in view of the prior art runs contrary to the arguments in support of validity that Mr. Snader and Mr. Maebius made during the prosecution of the '327 patent. It specifically runs contrary to the arguments made during prosecution that the '327 patent with its much later filing date was non-obvious over the prior art.[277]

[276] *United Therapeutics Corp. v. Liquidia Techs., Inc.*, No. 2023-1805, 2023 WL 8794633 (Fed. Cir. Dec. 20, 2023).
[277] *See* Section V.I.

D. UTC's submission of these references in later filed patents further supports materiality of these references

266. U.S. Application Nos. 17/486,721 ("'721 application") and 17/707,651 ("'651 application"), like the '793 patent, are directed to a method of treating pulmonary hypertension by using an inhalation device comprising a formulation of treprostinil.[278] The '721 application and the application leading to the '793 patent are both continuations of U.S. App. No. 16/536,954, and the '651 application is a continuation of the '721 application.[279]

267. During the prosecution of the '721 and '651 applications, and before the notice of allowance was issued for the '327 patent, Mr. Maebius submitted numerous "Notification[s] of Related Proceedings" to the USPTO disclosing '793 IPR filings that contain allegations of unpatentability.[280] During his deposition, Mr. Maebius confirmed that "document[s] from a similar family" that contain "allegations of unpatentability" would be disclosed to the USPTO during prosecution.[281]

268. In my opinion, UTC's disclosure of allegations of unpatentability during the prosecution of the '721 and '651 applications and Mr. Maebius' confirmation that such documents would be submitted during prosecution, further demonstrate the materiality of these allegations to the USPTO's patentability determination for all applications directed at related subject matter.

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[278] *See* UTC_PH-ILD_009772 at -796 (claim 1); LIQ_PH-ILD_00147360; LIQ_PH-ILD_00147453.
[279] *See* UTC_PH-ILD_009772; LIQ_PH-ILD_00147377; LIQ_PH-ILD_00147455.
[280] *See, e.g.*, LIQ_PH-ILD_00147359 (UTC disclosing the Institution Decision for the '793 IPR, along with the Patent Owner's Preliminary Response to Petition and accompanying exhibits); LIQ_PH-ILD_00147437 (UTC disclosing the Petitioner's Reply and exhibits for the '793 IPR); LIQ_PH-ILD_00147452 (UTC disclosing Institution Decision for the '793 IPR, along with the Patent Owner's Preliminary Response to Petition and accompanying exhibits, Petitioner's Reply and exhibits, and Patent Owner's Sur-Reply and exhibits); LIQ_PH-ILD_00147486 (UTC disclosing the Final Written Decision for the '793 IPR)
[281] Maebius Dep. Tr. at 85:10-86:5.

X. RESERVATION OF RIGHTS

269. This report is based on information currently available to me. I reserve the right to continue, update, and expand my investigation and analysis in a supplemental report if additional documents, deposition transcripts, or any other information is produced by UTC. I reserve the right to respond to any matters raised by Liquidia, or any opinions or conclusions of any expert, by relying on documents or other information that is additional to the information considered and cited herein. I further reserve the right to prepare exhibits to summarize and demonstrate my testimony at trial, and to supplement my opinions as permitted by any Court order.

I declare under penalty of perjury that the foregoing is true and correct.

Dated: December 19, 2024

Dr. Nicholas Hill

EXHIBIT 19

US011826327B2

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(54) **TREATMENT FOR INTERSTITIAL LUNG DISEASE**

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(57) **ABSTRACT**

Methods of treating of interstitial lung disease, reducing pulmonary function decline in a subject with interstitial lung disease (ILD), and increasing forced vital capacity (FVC) in a subject suffering from ILD are provided, wherein the methods include administration of treprostinil.

19 Claims, 15 Drawing Sheets

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Watson Laboratories, Inc. (Petitioner) v. *United Therapeutics, Inc.* (Patent Owner), Petition for Inter Partes Review, IRP2017-01622, U.S. Pat. No. 9,339,507, with all Exhibits on exhibit list.
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Welsh, Erin T., Ma, "Inhaled treprostinil improves outcomes in ILD-associated pulmonary hypertension," Jun. 30, 2020, 2 pages, www.healio.com/news/pulmonology/20200630/inhaled-treprostinil-improves-outcomes-in-ildassociated-pulmonary-hypertension.
Welsh, Erin T., Ma., FDA approves inhaled treprostinil for pulmonary hypertension associated with ILD, Apr. 5, 2021, www.healio.com/news/pulmonology/20210405/fda-approves-inhaled-treprostinil-for-pulmonary-hypertension-associated-with-ild.
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Ziegler et al., "Comparison of Cascade Impaction and Laser Diffraction for Particle Size Distribution Measurements," Journal of Aerosol Medicine, 2005, 18(3):311-324.
Zierenberg et al., "The Respimat, a New Soft Mist Inhaler for Delivering Drugs to the Lungs," Modified-Release Drug Delivery Technology, 2002, Chapter 78, 925-933.

* cited by examiner

Figure 1

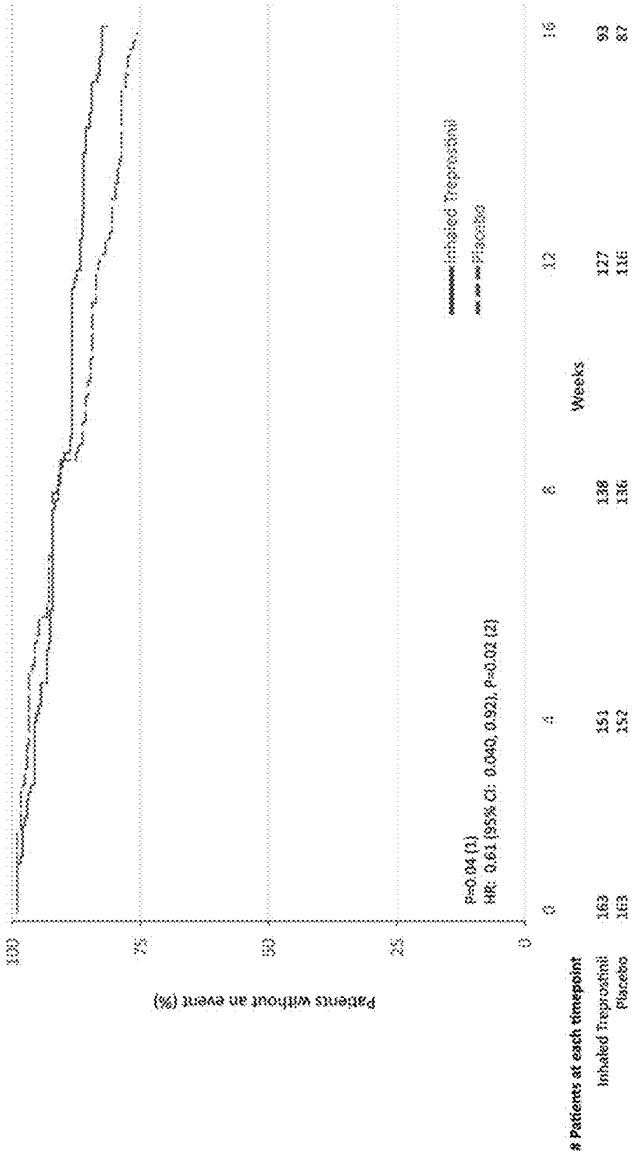

Patients without an event (%)
100
75
50
25
0
Inhaled Treprostinil
Placebo
P=0.04 (1)
HR: 0.61 (95% CI: 0.040, 0.92), P=0.02 (2)
0
4
8
12
16
Weeks
Patients at each timepoint
Inhaled Treprostinil 163 151 138 127 93
Placebo 163 152 136 116 87

Figure 2

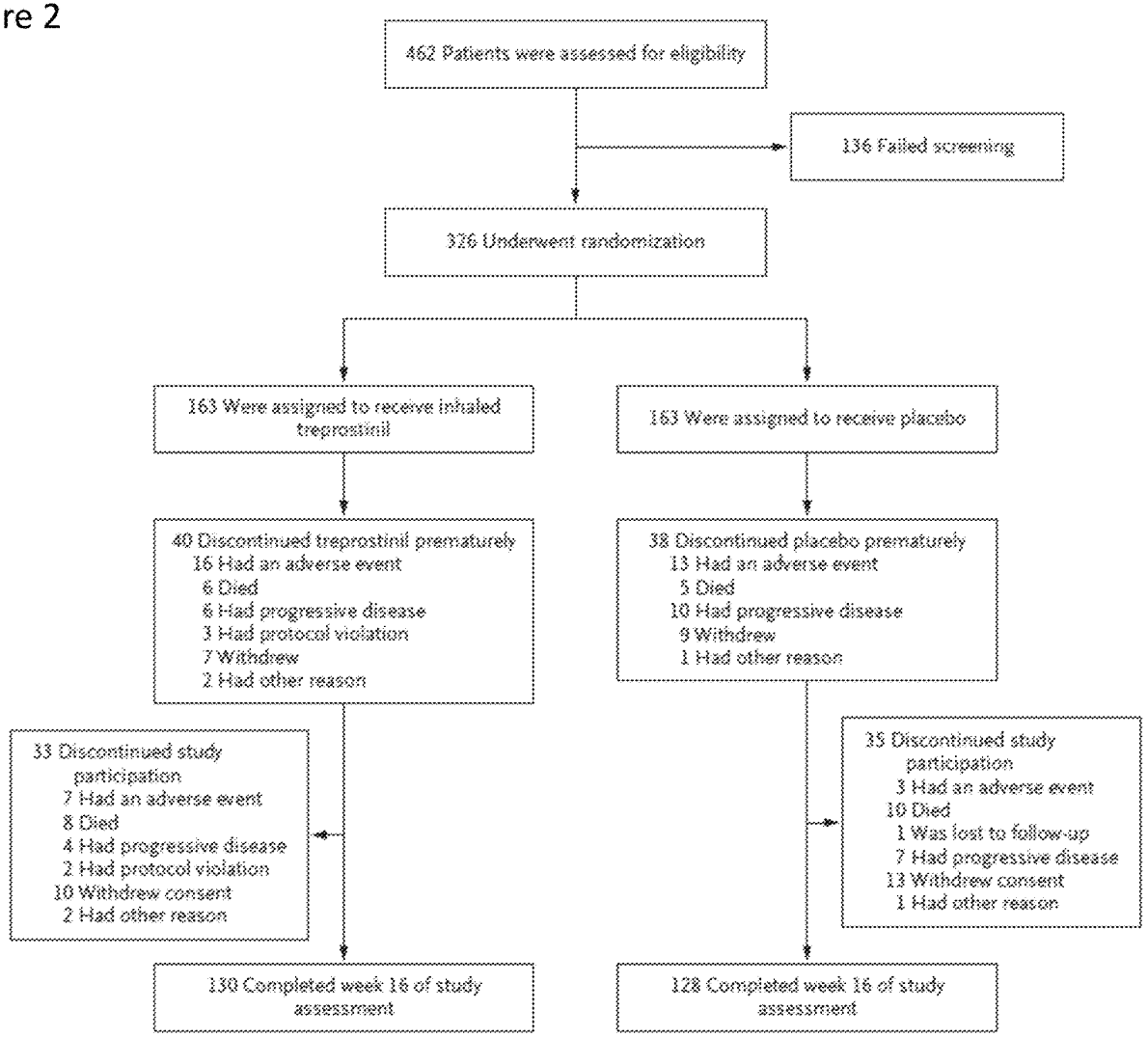

462 Patients were assessed for eligibility
136 Failed screening
326 Underwent randomization
163 Were assigned to receive inhaled treprostinil
163 Were assigned to receive placebo
40 Discontinued treprostinil prematurely
16 Had an adverse event
6 Died
6 Had progressive disease
3 Had protocol violation
7 Withdrew
2 Had other reason
38 Discontinued placebo prematurely
13 Had an adverse event
5 Died
10 Had progressive disease
9 Withdrew
1 Had other reason
33 Discontinued study participation
7 Had an adverse event
8 Died
4 Had progressive disease
2 Had protocol violation
10 Withdrew consent
2 Had other reason
35 Discontinued study participation
3 Had an adverse event
10 Died
1 Was lost to follow-up
7 Had progressive disease
13 Withdrew consent
1 Had other reason
130 Completed week 16 of study assessment
128 Completed week 16 of study assessment

Figure 3

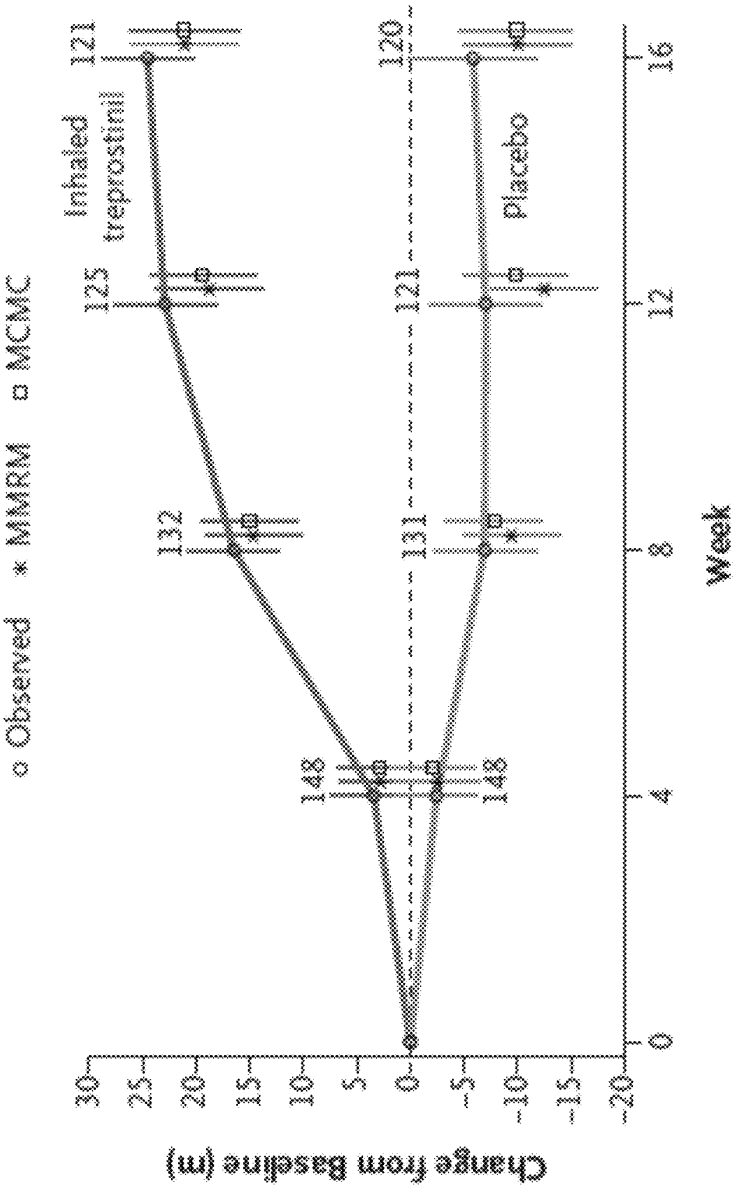

Observed
MMRM
MCMC
Inhaled treprostinil
Placebo
Change from Baseline (m)
Week
30
25
20
15
10
5
0
-5
-10
-15
-20
0
4
8
12
16
148
132
125
121
148
131
121
120

Figure 4


Change from baseline (m)
35
30
25
20
15
10
5
0
5.32
Week 4
24.13
Week 8
P<0.001
31.29
Week 12
P<0.001
31.12
Week 16

Figure 5

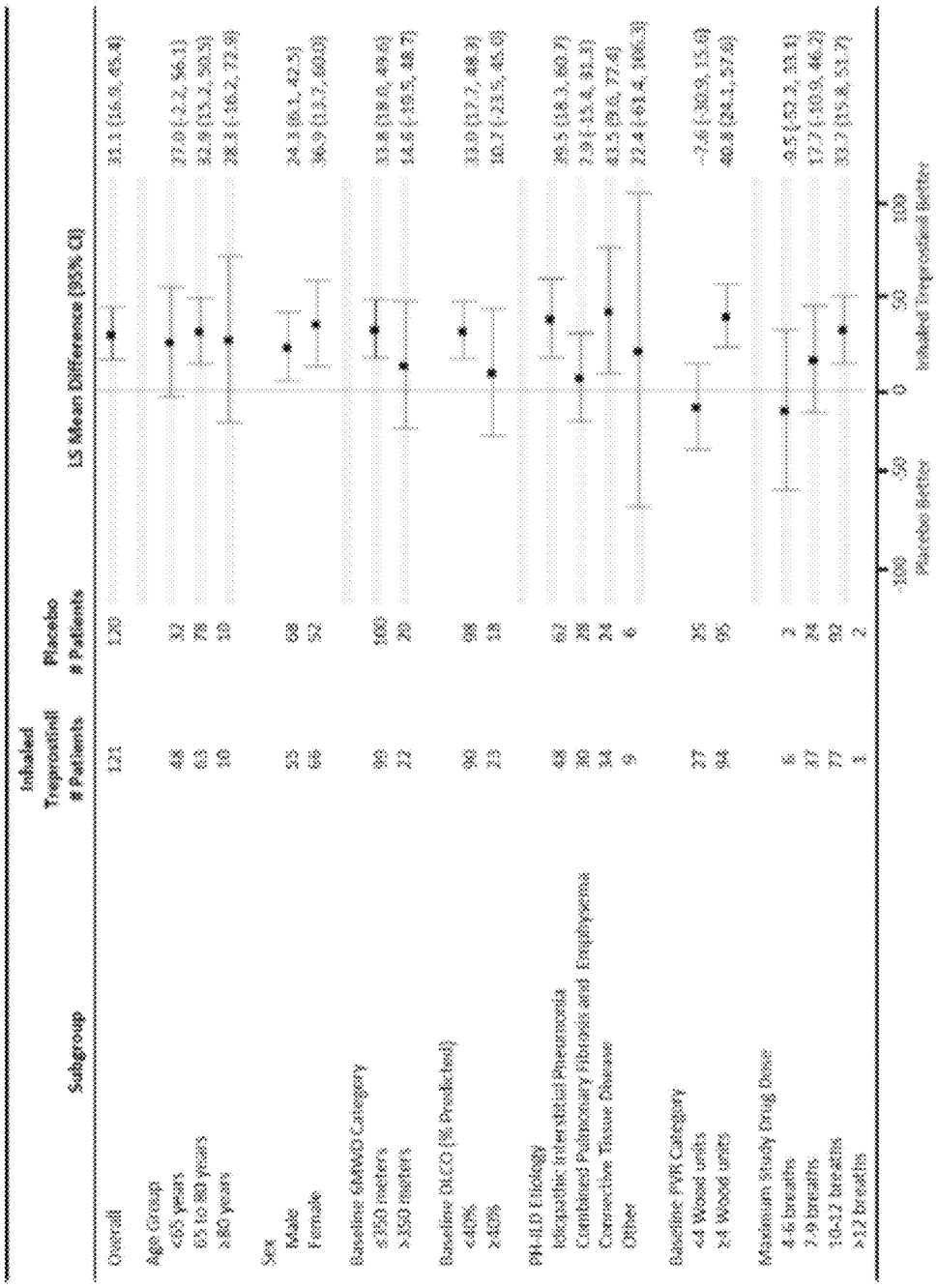

Subgroup
Inhaled Treprostinil # Patients
Placebo # Patients
LS Mean Difference (95% CI)
Overall 121 120 31.1 (16.6, 45.6)
Age Group
<65 years 48 52 27.0 (2.2, 56.1)
65 to 80 years 63 58 22.9 (3.2, 50.2)
>80 years 10 10 28.1 (-10.2, 72.8)
Sex
Male 53 68 24.3 (0.1, 42.5)
Female 68 52 36.9 (13.7, 60.0)
Baseline 6MWD Category
≤250 meters 99 98 33.8 (18.0, 49.6)
>250 meters 22 22 14.6 (-19.5, 48.7)
Baseline DLCO (% Predicted)
<40% 90 88 31.0 (12.7, 49.3)
≥40% 31 33 30.7 (-2.5, 63.9)
PH-ILD Etiology
Idiopathic Interstitial Pneumonia 68 62 39.5 (18.3, 60.7)
Combined Pulmonary Fibrosis and Emphysema 38 38 1.9 (-15.4, 19.3)
Connective Tissue Disease 14 14 43.5 (9.0, 77.9)
Other 6 6 22.4 (-61.4, 106.3)
Baseline PVR Category
<4 Wood units 27 25 -7.4 (-30.9, 16.0)
≥4 Wood units 94 95 40.8 (24.1, 57.6)
Magnitude Study Drug Dose
4-6 breaths 6 7 -9.5 (-52.3, 33.3)
7-9 breaths 22 24 17.7 (-5.9, 41.2)
10-12 breaths 27 29 33.7 (15.8, 51.7)
≥13 breaths 1 2
-100
-50
0
50
100
Favors Better
Inhaled Treprostinil Better

Figure 6

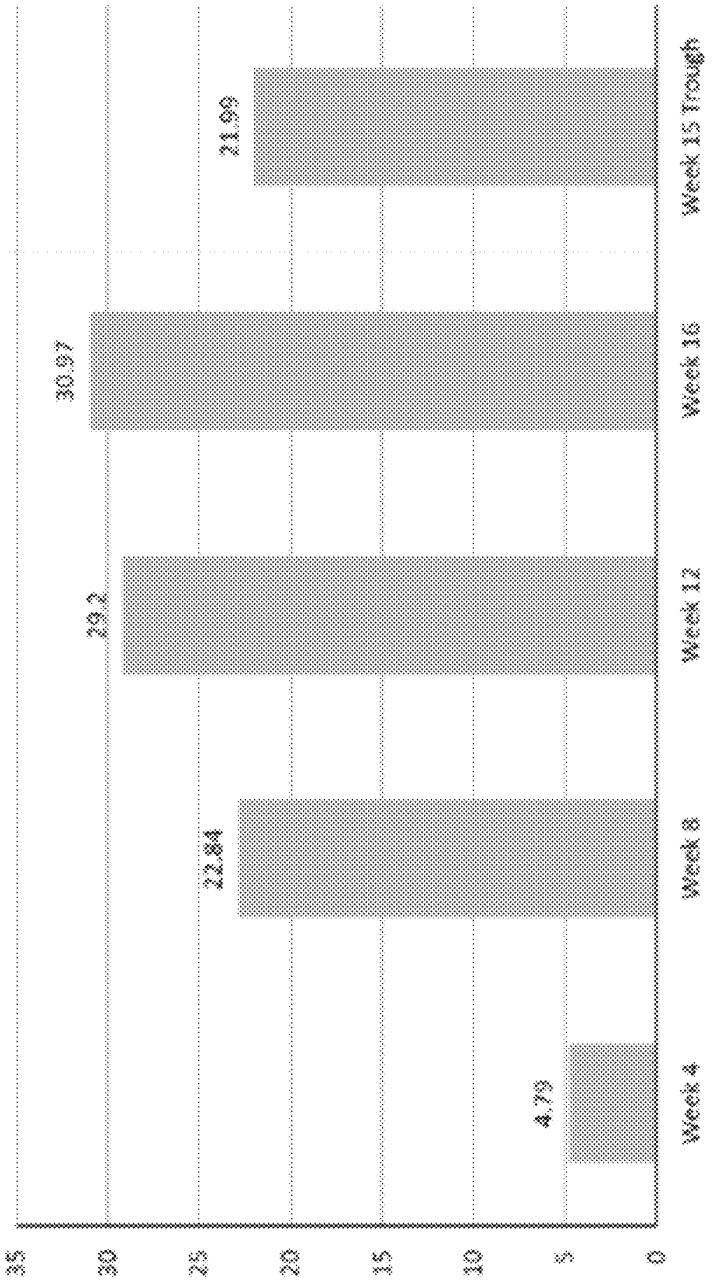

35
30
25
20
15
10
5
0
4.79
22.84
29.2
30.97
21.99
Week 4
Week 8
Week 12
Week 16
Week 15 Trough

Figure 7

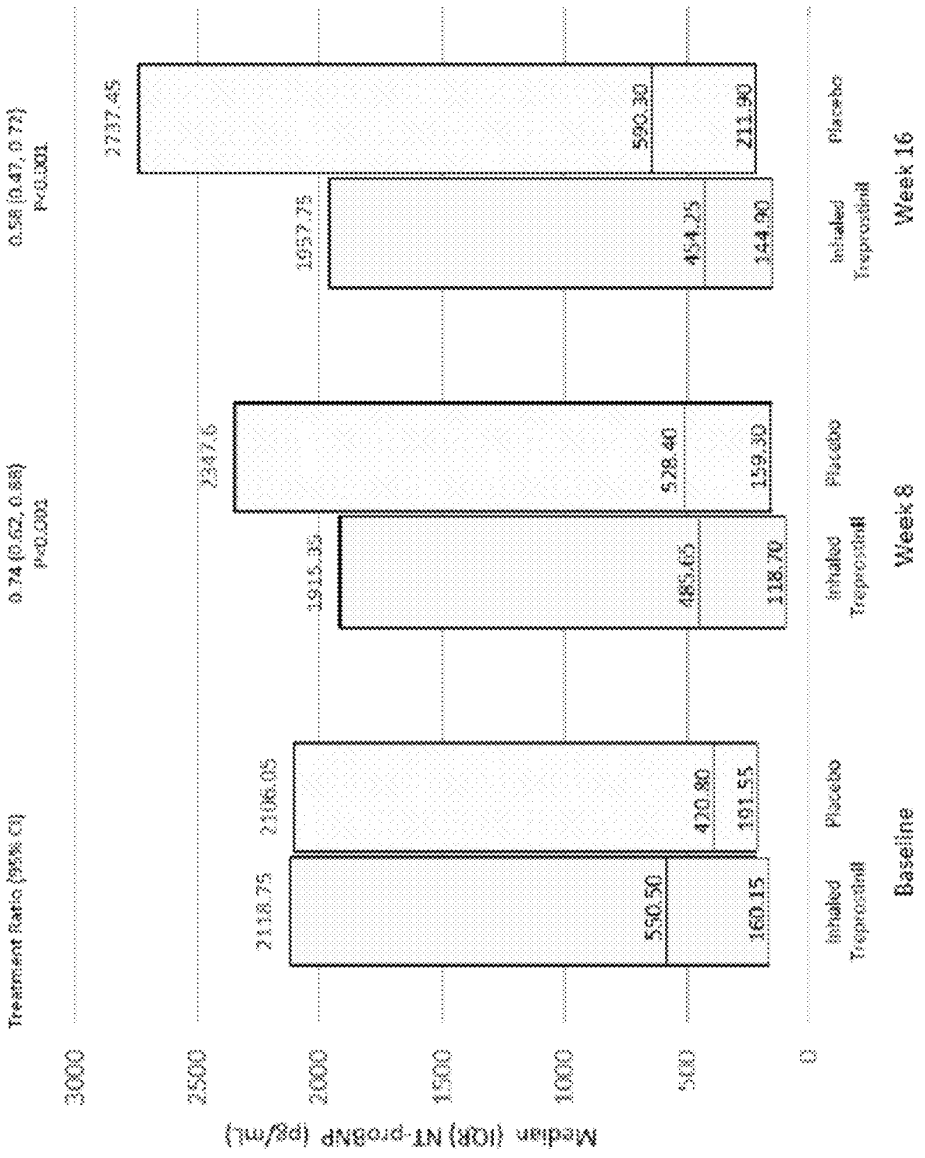
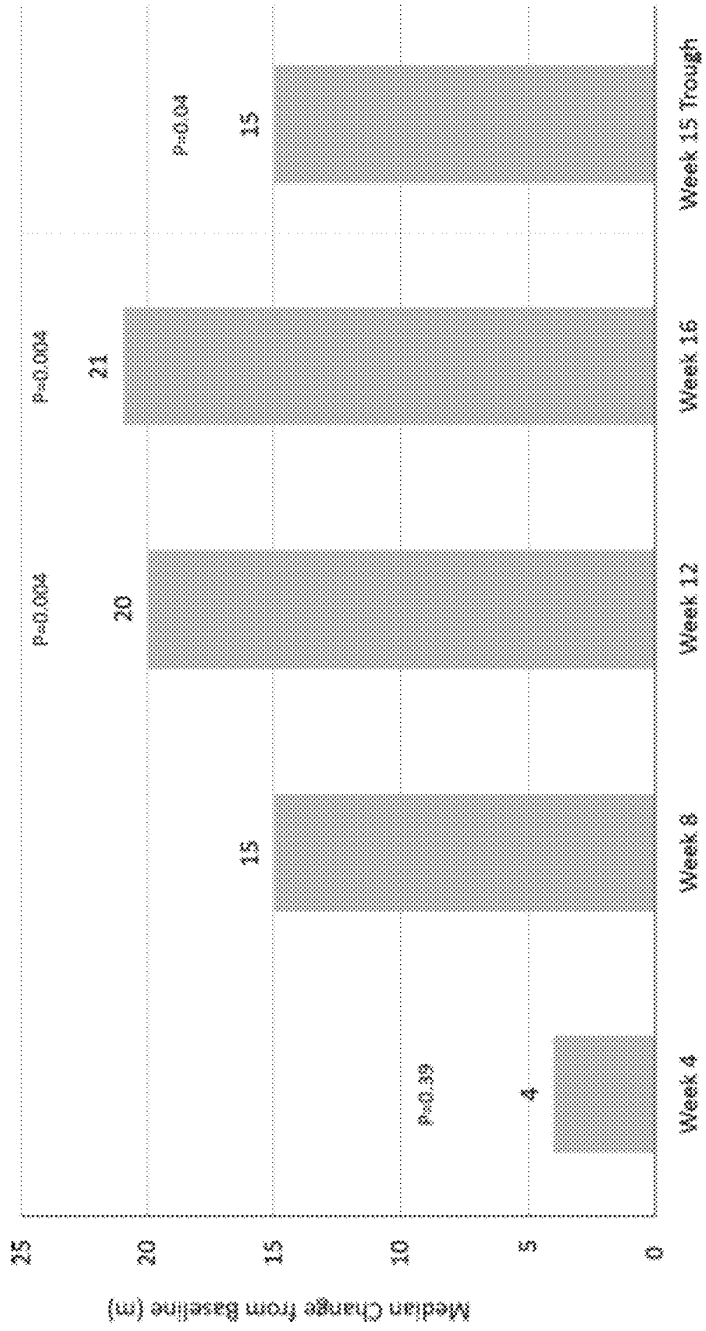

Median (IQR) NT-proBNP (pg/mL)
3000
2500
2000
1500
1000
500
0
Treatment Ratio (95% CI)
Baseline
Week 8
Week 16
Inhaled Treprostinil
Placebo
2118.75
530.50
160.15
2186.05
420.80
191.55
1915.30
485.05
118.70
2247.6
528.40
159.30
1957.75
414.25
144.90
2737.45
590.30
211.90
0.74 (0.62, 0.88) P<0.001
0.58 (0.47, 0.72) P<0.001

Figure 8


Median Change from Baseline (m)
25
20
15
10
5
0
Week 4
4
P=0.39
Week 8
15
Week 12
20
P=0.004
Week 16
21
P=0.004
Week 15 Trough
15
P=0.04

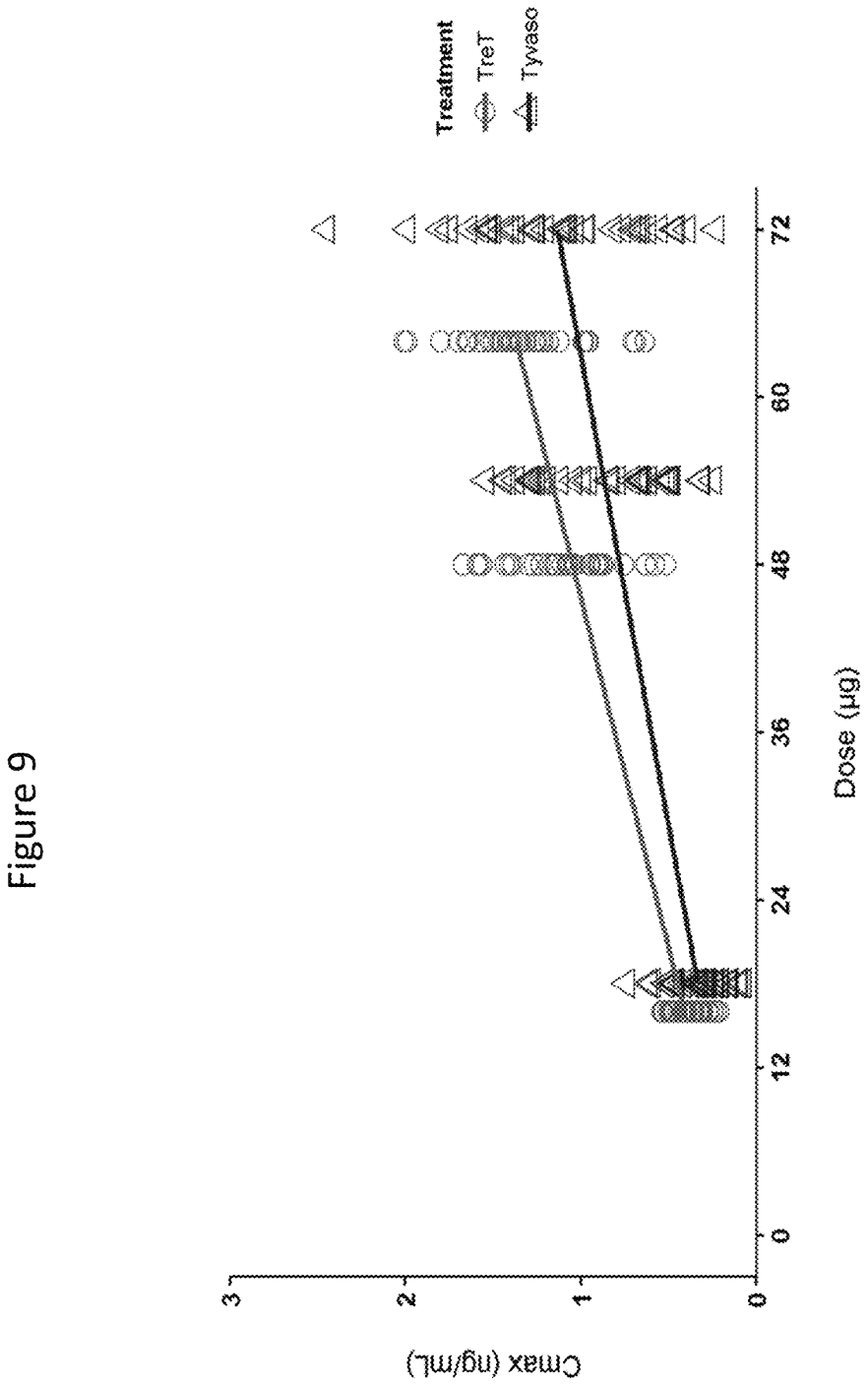

Treatment
TreT
Tyvaso
Cmax (ng/mL)
0
1
2
3
Dose (µg)
0
12
24
36
48
60
72

Figure 9

Figure 10

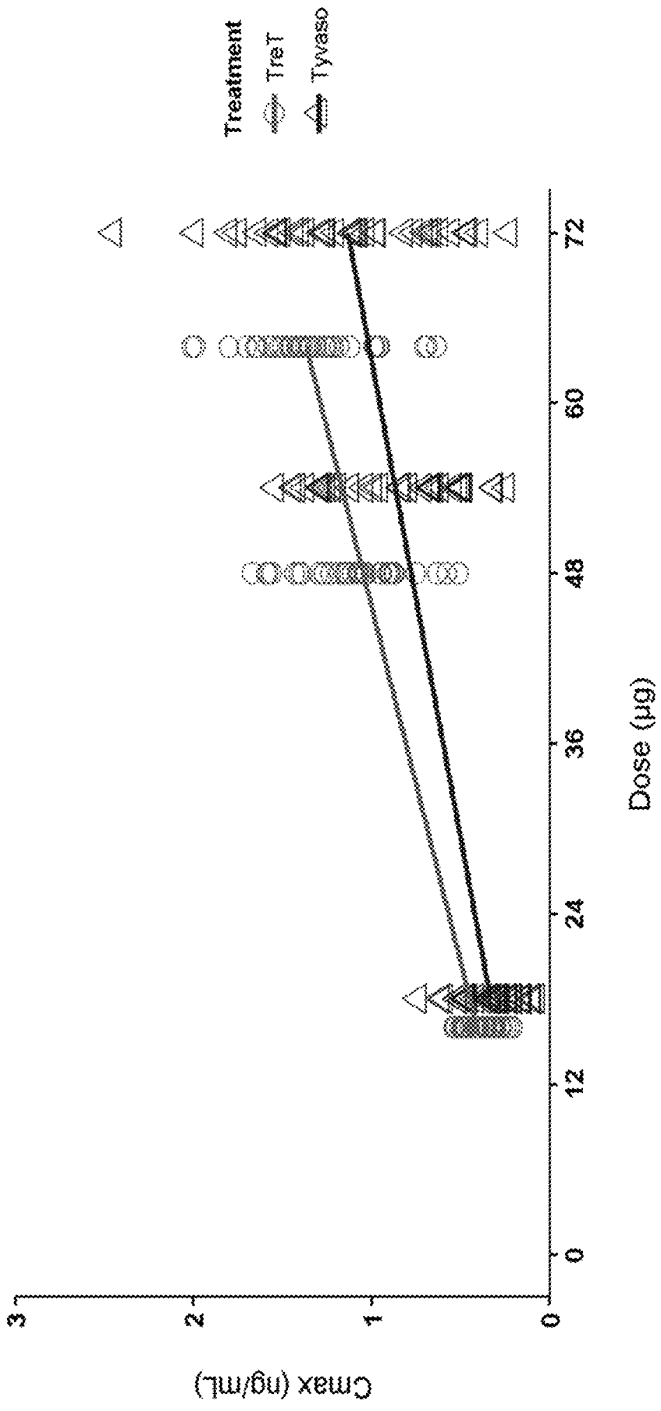

Treatment
TreT
Tyvaso
Cmax (ng/mL)
0
1
2
3
Dose (µg)
0
12
24
36
48
60
72

Figure 11

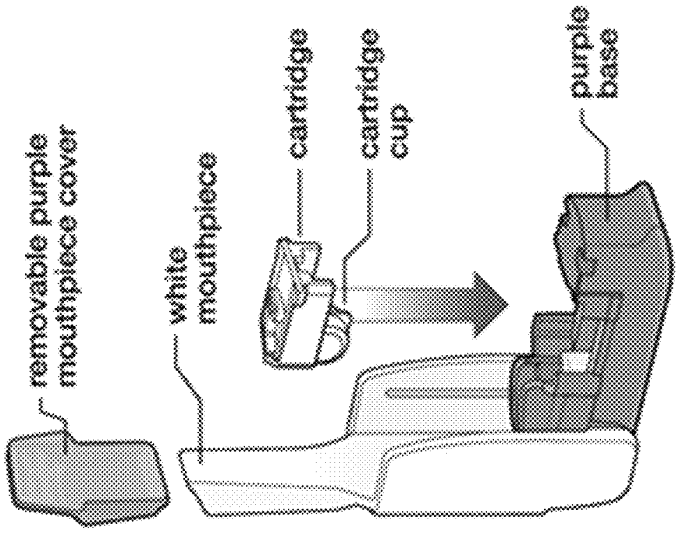

removable purple mouthpiece cover
white mouthpiece
cartridge
cartridge cup
purple base

Figure 12

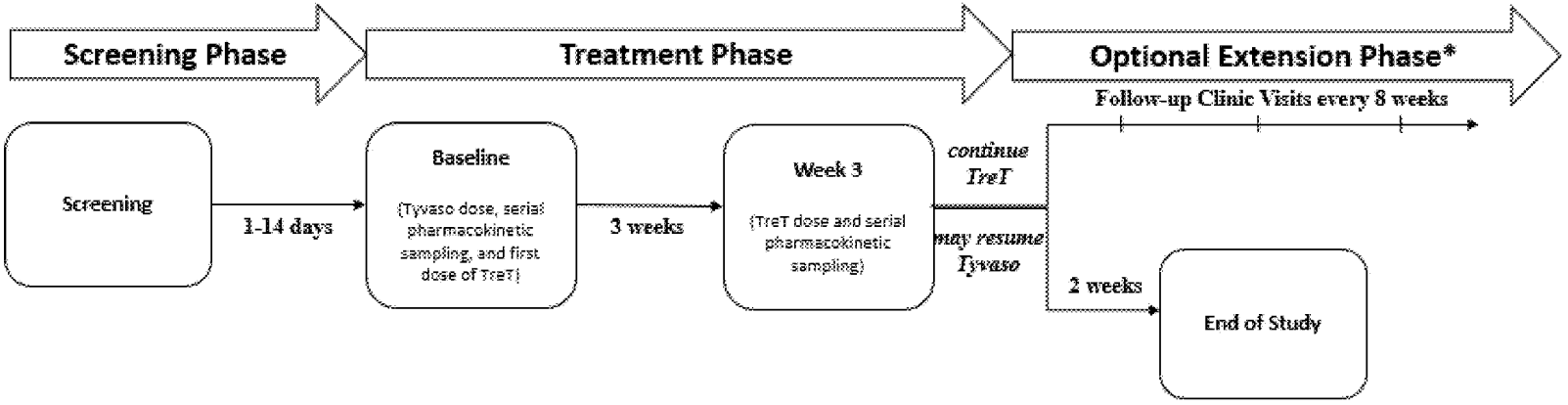

Screening Phase
Treatment Phase
Optional Extension Phase*
Follow-up Clinic Visits every 8 weeks
Screening
1-14 days
Baseline
(Tyvaso dose, serial pharmacokinetic sampling, and first dose of TreT)
3 weeks
Week 3
(TreT dose and serial pharmacokinetic sampling)
continue TreT
may resume Tyvaso
2 weeks
End of Study

Figure 13


Patients
25
20
15
10
5
0
21
18
6
2
1
1
48
64
60
96
144
180
Dose Strength

Figure 14

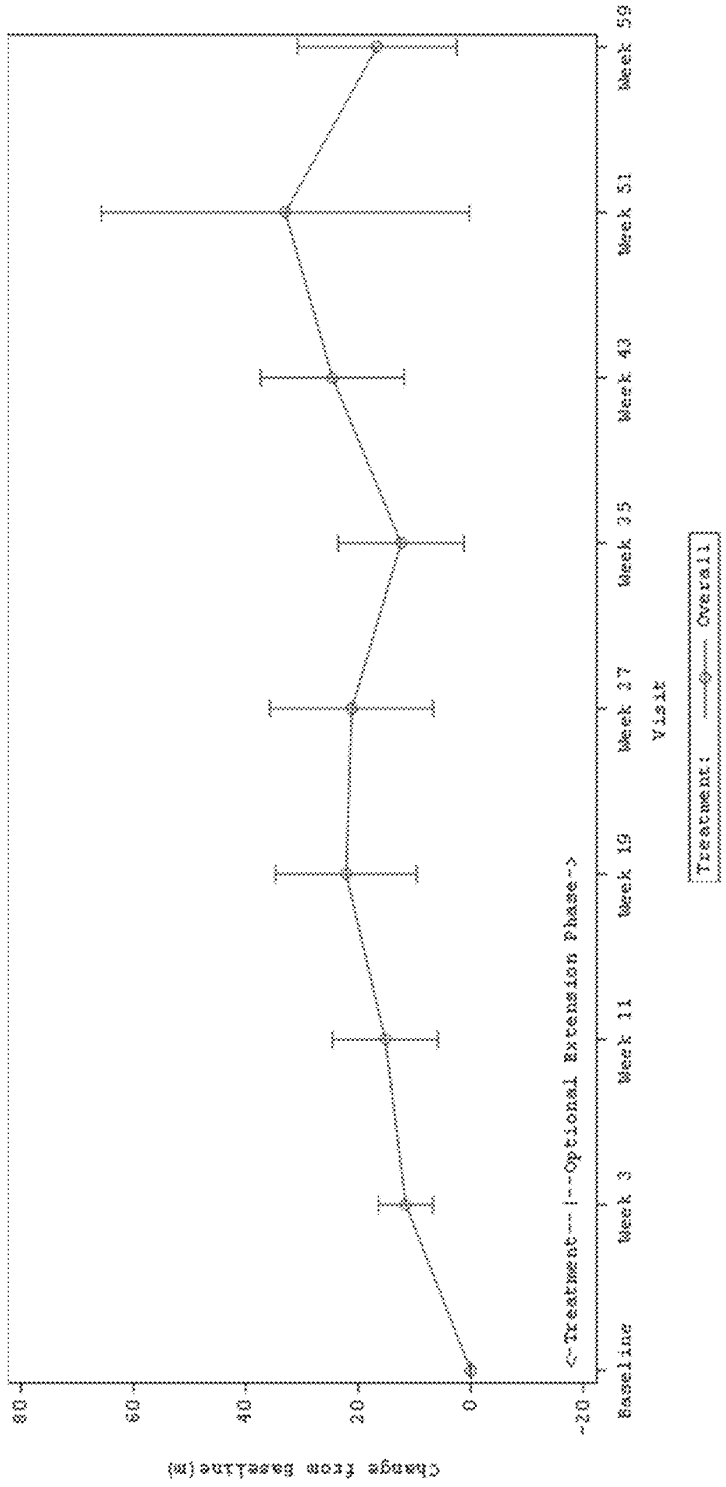
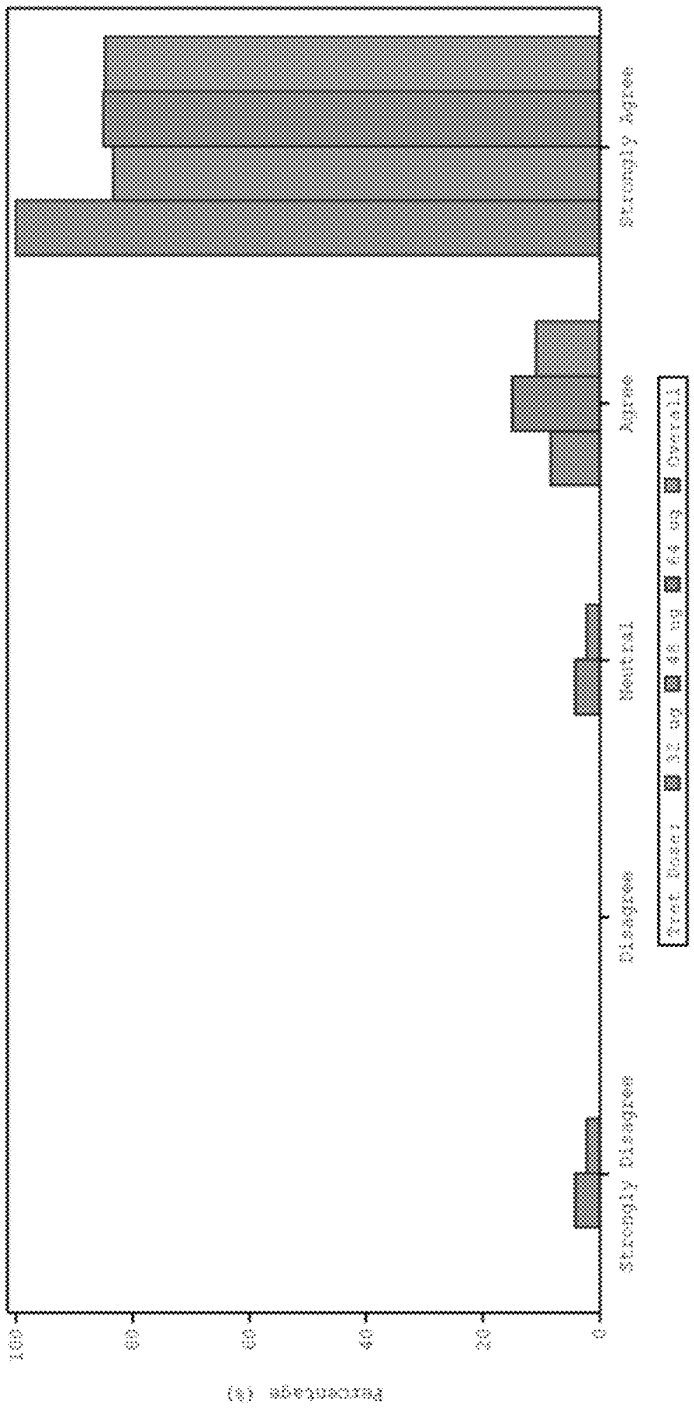

Change from Baseline(%)
80
60
40
20
0
-20
<-Treatment--|--Optional Extension Phase->
Baseline
Week 3
Week 11
Week 19
Week 27
Week 35
Week 43
Week 51
Week 59
Visit
Treatment: Overall

Figure 15


Strongly Agree
Agree
Neutral
Disagree
Strongly Disagree
First Count
Overall
Percentage (%)
0
20
40
60
80
100

TREATMENT FOR INTERSTITIAL LUNG DISEASE

RELATED APPLICATIONS

The present application claims priority to U.S. provisional application No. 63/011,810 filed Apr. 17, 2020 and U.S. provisional application No. 63/160,611 filed Mar. 12, 2021, each of which is incorporated herein by reference in its entirety.

FIELD

The present application generally relates to methods of treating a disease with prostacyclins and more particularly, to treating a disease with treprostinil.

BACKGROUND

Interstitial lung disease (ILD), or diffuse parenchymal lung disease (DPLD), is a group of lung diseases affecting the interstitium (the tissue and space around the alveoli, including air sacs of the lungs). It concerns alveolar epithelium, pulmonary capillary endothelium, basement membrane, and perivascular and perilymphatic tissues. It may occur when an injury to the lungs triggers an abnormal healing response. Such abnormal response may result in idiopathic pulmonary fibrosis (IPF). Currently, two drugs are approved by FDA for treatment of IPF, which is the most common form of PF: nintedanib and pirfenidone. The average rate of survival for someone with interstitial lung disease is currently between 3 and 5 years (Meyer et al., 2017). There exists a need for the identification of new pharmaceutical treatments for ILD.

SUMMARY

In one aspect, a method of treating a pulmonary hypertension due to a condition which is selected from a chronic lung disease, hypoxia and a combination thereof, comprises administering to a subject having the pulmonary hypertension due to the condition selected from a chronic lung disease, hypoxia and a combination thereof an effective amount of treprostinil, a prodrug thereof or a pharmaceutically acceptable salt thereof.

In one aspect, a method of treating interstitial lung disease (ILD) in a subject in need thereof is provided, comprises administering to the subject a therapeutically effective amount of treprostinil, a prodrug, salt, or ester thereof. In an embodiment, the subject has pulmonary hypertension associated with ILD.

In one aspect, a method of reducing pulmonary function decline in a subject with ILD is provided, comprises administering to the subject treprostinil, a prodrug, salt, or ester thereof.

In one aspect, a method of increasing forced vital capacity (FVC) in a subject suffering from ILD is provided, comprises administering to the subject treprostinil, a prodrug, salt, or ester thereof. In some embodiments, administration of treprostinil, a prodrug, salt, or ester thereof may result in an increase of FVC of at least 20%, at least 40%, at least 60%, at least 80%, at least 90%, or at least 100% compared to the FVC prior to the start of treatment. The FVC can be assessed prior to the start of treatment and at intervals after the start of treatment. For example, the pre-treatment FVC can be compared to the FVC measured at one week, four weeks, eight weeks, or sixteen weeks after the start of treatment.

In some embodiments, administering an effective amount of treprostinil, its prodrug, its pharmaceutically acceptable salt or a pharmaceutically acceptable salt of its prodrug may provide an improvement, which may be statistically significant, in forced vital capacity (FVC) in a subject with a condition selected from a chronic lung disease, such as an ILD or IPF and/or hypoxia. For example, the FVC may be higher in a patient subpopulation with the chronic lung disease and/or hypoxia, who was administered the effective amount of treprostinil, its prodrug, its pharmaceutically acceptable salt or a pharmaceutically acceptable salt of its prodrug for at least 4 weeks, at least 5 weeks, at least 6 weeks, at least 7 weeks, at least 8 weeks, at least 9 weeks, at least 10 weeks, at least 11 weeks, at least 12 weeks, at least 13 weeks, at least 14 weeks, at least 15 weeks or at least 16 weeks or at least 20 weeks or at least 24 weeks, or at least 28 weeks or at least 32 weeks, or at least 36 weeks or at least 40 weeks or at least 44 weeks or at least 48 weeks or at least 52 weeks, compared to a patient subpopulation with the same condition, which was administered a placebo instead of treprostinil. For example, the FVC value may be higher by at least 10 ml or at least 15 ml or at least 20 ml or at least 25 ml or at least 30 ml or at least 35 ml or at least 40 ml or at least 45 ml after at least 4 weeks, at least 5 weeks, at least 6 weeks, at least 7 weeks, at least 8 weeks, at least 9 weeks, at least 10 weeks, at least 11 weeks, at least 12 weeks, at least 13 weeks, at least 14 weeks, at least 15 weeks or at least 16 weeks of the administering in the patient subpopulation with the chronic lung disease and/or hypoxia, who was administered the effective amount of treprostinil, its prodrug, its pharmaceutically acceptable salt or a pharmaceutically acceptable salt of its prodrug compared to the patient subpopulation with the same condition, which was administered a placebo instead of treprostinil. In patients with a chronic lung disease, such as interstitial lung disease, and/or hypoxia, an FVC value usually decreases with time when untreated. Thus, administering the effective amount of treprostinil, its prodrug, its pharmaceutically acceptable salt or a pharmaceutically acceptable salt may increase an FVC value compared to an FVC value before the administering; maintain an FVC value within 5%, 10% or 20% within the FVC value prior to the administering; or reduce a decrease of an FVC value with time compared to a decrease in an FVC value with no administering the effective amount of treprostinil, its prodrug, its pharmaceutically acceptable salt or a pharmaceutically acceptable salt, such a decrease in an FVC value when placebo is administered instead of treprostinil, its prodrug, its pharmaceutically acceptable salt or a pharmaceutically acceptable salt.

In some embodiments, the ILD comprises one or more of idiopathic pulmonary fibrosis (IPF), desquamative interstitial pneumonia (DIP), acute interstitial pneumonia (AIP), nonspecific interstitial pneumonia (NSIP), respiratory bronchiolitis-associated interstitial lung disease (RB-ILD), cryptogenic organizing pneumonia (COP), lymphoid interstitial pneumonia (LIP), sarcoidosis, rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, polymyositis, dermatomyositis, antisynthetase syndrome, silicosis, asbestosis, occupational lung disease, chronic hypersensitivity pneumonitis, idiopathic interstitial pneumonia (IIP), an autoimmune ILD, lymphangioleiomyomatosis (LAM), Langerhan's cell histiocytosis (LCH), drug associated ILD, vasculitis, granulomatosis, and berylliosis. In some embodiments, the ILD comprises IPF.

In some embodiments, the ILD comprises systemic sclerosis-associated interstitial lung disease (SSc-ILD).

In some embodiments, the ILD was induced from antibiotics, chemotherapy, antiarrhythmic agents, coronavirus disease 2019 (COVID-19), atypical pneumonia, pneumocystis pneumonia, tuberculosis (TB), *Chlamydia trachomatis*, respiratory syncytial virus, or lymphangitic carcinomatosis.

In some embodiments, the subject has one or more of surfactant-protein-B deficiency, surfactant-protein-C deficiency, ABCA3-deficiency, brain lung thyroid syndrome, congenital pulmonary alveolar proteinosis, alveolar capillary dysplasia, mutations in telomerase reverse transcriptase, mutations in telomerase RNA component, mutations in the regulator of telomere elongation helicase 1, and mutations in poly(A)-specific ribonuclease.

In some embodiments, the subject has one or more symptoms of shortness of breath, fatigue, weight loss, dry cough, chest pain, and lung hemorrhage. In some embodiments, after administration the symptom is improved by about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, or about 100%, as measured by a medically-recognized technique. In some embodiments, the medically-recognized technique comprises one or more of Modified Medical Research Council (MMRC) Dyspnoea Scale, Modified Borg Dyspnoea Scale (0-10), Chalder Fatigue Scale, weight measurement scale, visual analogue scale (VAS) for cough, King's Brief Interstitial Lung Disease Questionnaire, Leicester Cough Questionnaire (LCQ), Living with IPF (L-IPF, see e.g. Am J Respir Crit Care Med Vol 202, Iss 12, pp 1689-1697, Dec. 15, 2020), computed tomography (CT) scan, X-ray, multiple magnetic resonance imaging (MRI), pulmonary function testing (PFT), spirometry, lung volumes, maximal respiratory pressure, diffusing capacity, oxygen desaturation, and arterial blood gas evaluation.

In some embodiments, treprostinil, a prodrug, salt, or ester thereof is administered in a pharmaceutical composition comprising treprostinil, a prodrug, salt, or ester thereof and a pharmaceutically acceptable carrier or excipient.

In some embodiments, the administration comprises at least one of oral, inhalation, subcutaneous, nasal, intravenous, intramuscular, sublingual, buccal, rectal, vaginal, and transdermal administration. In some embodiments, the administration comprises inhalation. In some embodiments, one inhalation dosing event comprises from 1 to 20 breaths, wherein at least one inhalation dosing event per day is administered.

In some embodiments, the method comprises administration of at least one additional active agent to treat the ILD. In some embodiments, the at least one additional active agent comprises a corticosteroid, mycophenolic acid, mycophenolate mofetil, azathioprine, cyclophosphamide, rituximab, pirfenidone, or nintedanib. In some embodiments, the at least one additional active agent and treprostinil, a prodrug, salt, or ester thereof, are administered via a method selected from the group consisting of (a) concomitantly; (b) as an admixture; (c) separately and simultaneously or concurrently; and (d) separately and sequentially.

In some embodiments, administration is once, twice, thrice, four times, five times, or six times per day. In some embodiments, administration is for a period selected from the group consisting of about 1 day, about 1 day to about 3 days, about 3 days to about 6 days, about 6 days to about 9 days, about 9 days to about 12 days, about 12 days to about 15 days, about 15 days to about 18 days, about 18 days to about 21 days, about 21 days to about 24 days, about 24 days to about 27 days, about 27 days to about 30 days, or about greater than 30 days.

In some embodiments, a method of treating a pulmonary hypertension due to a condition which is selected from a chronic lung disease, hypoxia and a combination thereof, comprises administering to a subject having the pulmonary hypertension due to the condition selected from a chronic lung disease, hypoxia and a combination thereof an effective amount of treprostinil, a prodrug thereof or a pharmaceutically acceptable salt thereof.

In some embodiments, the subject is a human.

FIGURES

FIG. **1** shows a Kaplan-Meier plot of time to exacerbation of underlying lung disease over a 16-week period of treprostinil treatment. CI stands for confidence interval; HR stands for hazard ratio. Subjects who discontinued from the study early had their time to first clinical worsening event censored at their last visit. Subjects who did not experience a clinical worsening event had their time to first clinical worsening event censored at the study termination date. (1) P-value was calculated with log-rank test stratified by baseline 6-minute walk distance category. (2) Hazard ratio, 95% CI, and p-value were calculated with proportional hazards model with treatment and baseline 6-minute walk distance (continuous) as explanatory variables.

FIG. **2** outlines a plan for the clinical study presented in Example 3. Of 462 patients screened for eligibility, 326 patients underwent randomization and received at least one dose of the assigned treprostinil or placebo (included in the intention-to-treat and safety populations). Of the patients who underwent randomization, 40 patients in the treprostinil group and 38 in the placebo group discontinued the assigned regimen prematurely. These patients were not withdrawn from the trial but were encouraged to remain and complete assessments through week 16; 33 patients in the treprostinil group and 35 in the placebo group discontinued trial participation before week 16.

FIG. **3** shows mean change from baseline in peak 6-minute walking distance through week 16 in the clinical study presented in Example 3. Shown are mean (±SE) changes from baseline (dashed line) in peak 6-minute walk distance over the 16-week trial period. The data shown are for patients with available data (observed) as well as for the results of two analysis methods used to account for missing data. The values shown at each data point indicate the number of patients assessed at that time point. The primary analysis used mixed-model repeat-measurement (MMRM) methods, with the assumption that missing data were missing at random. The model included the change from baseline to peak 6-minute walk distance as the dependent variable, with treatment, week, and treatment-by-week interaction as fixed effects, and the baseline 6-minute walk distance as a covariate. A sensitivity analysis for the primary end point was performed with the use of a multiple imputation approach with a multivariate normal imputation model using the Markov chain Monte Carlo (MCMC) method. The imputation model included treatment group, all scheduled visits, patient's sex, and patient's age at randomization. The confidence intervals have not been adjusted for multiplicity and cannot be used to infer definitive treatment effects.

FIG. **4** shows 6-Minute Walk Distance Treatment Effect Using Mixed Model Repeated Measurement Through Week 16. A longitudinal data analysis using mixed model repeated

measurement was also performed to estimate the treatment difference in change in peak 6-minute walk distance at Week 16. The mixed model repeated measurement includes the change from baseline in peak 6-minute walk distance as the dependent variable; treatment, week, and treatment by week interaction as fixed effects; and baseline 6-minute walk distance as a covariate. An unstructured variance/covariance structure shared across treatment groups was used to model the within-subject errors.

FIG. **5** shows Forest Plot on Subgroup Analyses of Peak 6-Minute Walk Distance (meter) at Week 16. 6MWD stands for 6-minute walk distance; CI stands for confidence interval; ILD stands for interstitial lung disease; PH stands for pulmonary hypertension; PVR stands for pulmonary vascular resistance; LS mean differences and their 95% confidence intervals, and p-values are from the mixed model repeated measures. The confidence intervals have not been adjusted for multiplicity and cannot be used to infer definitive treatment effects. For etiology, the "other" category includes chronic hypersensitivity pneumonitis and occupational lung disease.

FIG. **6** shows 6-Minute Walk Distance Treatment Effect Using Multiple Imputation Through Week 16. Multiple imputation approach using a multivariate normal imputation model with the Markov Chain Monte Carlo method. P-values are obtained from 100 multiple imputations using Markov Chain Monte Carlo estimation with ANCOVA model with change from Baseline in 6-minute walk distance as the dependent variable, treatment as fixed effect, and Baseline 6-minute walk distance measurement as a covariate.

FIG. **7** shows NT-proBNP Results by Study Visit (pg/mL). CI stands for confidence interval; IQR stands for interquartile range; NT-proBNP stands for N-terminal pro-brain natriuretic peptide. As displayed above, inhaled treprostinil was associated with a 42% reduction in NT-proBNP compared to placebo at Week 16 (Treatment Ratio 0.58; 95% CI: 0.47, 0.72; P<0.001). Only subjects with a Baseline NT-proBNP measurement are included in this analysis. P-values, estimated treatment ratio, and associated 95% CIs (LS Mean difference expressed as ratio) are obtained from the analysis of covariance with change from baseline in log transformed data in NT-proBNP as the dependent variable, treatment as the fixed effect, and log-transformed baseline NT-proBNP as a covariate. The confidence intervals have not been adjusted for multiplicity and cannot be used to infer definitive treatment effects.

FIG. **8** shows Hodges-Lehmann Estimate of Treatment Effect for 6-Minute Walk Distance Through Week 16. For those subjects who withdrew early due to death, were too ill to walk, or had no 6-minute walk distance measurement due to a clinical worsening event, the 6-minute walk distance was set to 0; for all other withdrawals without a measurement, last observation carried forward was used for imputation. P-values are obtained from nonparametric ANCOVA adjusted for Baseline 6-minute walk distance category.

FIG. **9** is a plot showing a relationship between treprostinil AUC0-5 and dose for Treprostinil Inhalation Powder (TreT) administered by a dry powder inhaler and nebulized treprostinil administered by Tyvaso nebulizer.

FIG. **10** is a plot showing a relationship between treprostinil Cmax and dose for Treprostinil Inhalation Powder (TreT) administered by a dry powder inhaler and nebulized treprostinil administered by Tyvaso nebulizer.

FIG. **11** shows a dry powder inhaler, which has a cartridge with a dose of Treprostinil Inhalation Powder (TreT).

FIG. **12** shows a design of a study of Example 5. During the Optional Extension Phase (OEP), dosing titration is encouraged; the dose of TreT is titrated upward, as clinically tolerated, to identify a maximum stable dose in each subject.

FIG. **13** shows a number of subjects for various maintenance TreT doses in the OEP.

FIG. **14** shows a change in 6 minute walk distance (6MWD) with respect to a baseline 6MWD as a function of duration of TreT treatment.

FIG. **15** is a plot reporting satisfaction of participants of the study of Example 5.

DETAILED DESCRIPTION

It is noted that, as used herein and in the appended claims, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. It is further noted that the claims may be drafted to exclude any optional element. As such, this statement is intended to serve as antecedent basis for use of such exclusive terminology as "solely," "only" and the like in connection with the recitation of claim elements or use of a "negative" limitation.

As used herein, the term "comprising" or "comprises" is intended to mean that the compositions and methods include the recited elements, but do not exclude others. A composition or method "consisting essentially" of the elements as defined herein would not exclude other materials or steps that do not materially affect the basic and novel characteristic(s) of the claimed technology. "Consisting of" shall mean excluding more than trace elements of other ingredients and substantial method steps. Embodiments defined by each of these transition terms are within the scope of this technology. When an embodiment is defined by one of these terms (e.g., "comprising") it should be understood that this disclosure also includes alternative embodiments, such as "consisting essentially of" and "consisting of" for said embodiment.

"Subject" refers to an animal, such as a mammal (including a human), that has been or will be the object of treatment, observation or experiment. "Subject" and "patient" may be used interchangeably, unless otherwise indicated. The methods described herein may be useful in human therapy and/or veterinary applications. In some embodiments, the subject is a mammal. In some embodiments, the subject is a human.

The terms "therapeutically effective amount," "effective amount," and "pharmaceutically effective amount" are used interchangeably and refer to an amount of a compound that is sufficient to effect treatment as defined below, when administered to a patient (e.g., a human) in need of such treatment in one or more doses. The therapeutically effective amount will vary depending upon the patient, the disease being treated, the weight and/or age of the patient, the severity of the disease, or the manner of administration as determined by a qualified prescriber or care giver. The therapeutically effective amount can be determined by titrating the dose upwards from a starting dose, either in terms of dose by administration or frequency of administration. In some embodiments, the therapeutically effective dose is determined by titrating the dose upwards until the maximum tolerated dose for the individual subject is determined.

The term "treatment" or "treating" means administering a compound disclosed herein for the purpose of (i) delaying the onset of a disease, that is, causing the clinical symptoms of the disease not to develop or delaying the development thereof, (ii) inhibiting the disease, that is, arresting the

development of clinical symptoms; and/or (iii) relieving the disease, that is, causing the regression of clinical symptoms or the severity thereof.

The term "pulmonary fibrosis" is a condition characterized by scarring and thickening of the lungs. Symptoms include shortness of breath, fatigue, weakness, chronic dry, hacking cough, loss of appetite, and discomfort in the chest. Eventually the scarring in the lung becomes replaced with fibrotic tissue resulting in loss of the lung's ability to transfer oxygen to the blood.

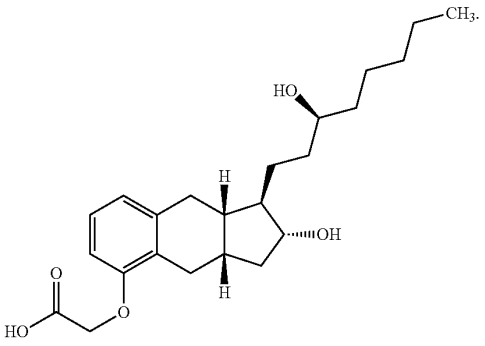
Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this present technology belongs. Although any methods and materials similar or equivalent to those described herein can also be used in the practice or testing of the present technology, representative illustrative methods and materials are described herein.

All numerical designations, e.g., pH, temperature, time, concentration, dose, and molecular weight, including ranges, are approximations which are varied (+) or (−) by increments of 0.05%, 1%, 2%, 5%, 10% or 20%. It is to be understood, although not always explicitly stated that all numerical designations are preceded by the term "about."

Where a range of values is provided, it is understood that each intervening value, to the tenth of the unit of the lower limit unless the context clearly dictates otherwise, between the upper and lower limit of that range and any other stated or intervening value in that stated range, is encompassed within the present technology. The upper and lower limits of these smaller ranges may independently be included in the smaller ranges and are also encompassed within the present technology, subject to any specifically excluded limit in the stated range. Where the stated range includes one or both of the limits, ranges excluding either or both of those included limits are also included in the present technology.

In an aspect, the present disclosure provides a method of treating interstitial lung disease (ILD) in a subject in need, comprising administering to the subject a therapeutically effective amount of treprostinil, a prodrug, salt, or ester thereof.

Treprostinil is used for the treatment of pulmonary arterial hypertension. Treprostinil is a synthetic analog of prostacyclin (PGI_2) having the structure:



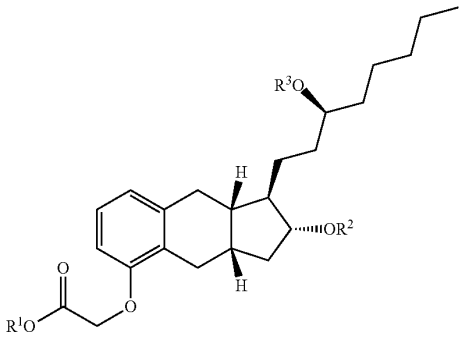
Treprostinil, the active ingredient in Remodulin® (treprostinil) Injection, Tyvaso® (treprostinil) Inhalation Solution, and Orenitram® (treprostinil) Extended Release Tablets, was described in U.S. Pat. No. 4,306,075. Methods of making treprostinil and other prostacyclin derivatives are described, for example, in Moriarty, et al., J. Org. Chem. 2004, 69, 1890-1902, Drug of the Future, 2001, 26(4), 364-374, U.S. Pat. Nos. 6,441,245, 6,528,688, 6,700,025, 6,809,223, 6,756,117, 8,461,393, 8,481,782; 8,242,305, 8,497,393, 8,940,930, 9,029,607, 9,156,786 and 9,388,154 9,346,738; U.S. Published Patent Applications Nos. 2012-0197041, 2013-0331593, 2014-0024856, 2015-0299091, 2015-0376106, 2016-0107973, 2015-0315114, 2016-0152548, and 2016-0175319; PCT Publications No. WO2016/0055819 and WO2016/081658.

Various uses and/or various forms of treprostinil are disclosed, for example, in U.S. Pat. Nos. 5,153,222, 5,234, 953, 6,521,212, 6,756,033, 6,803,386, 7,199,157, 6,054,486, 7,417,070, 7,384,978, 7,879,909, 8,563,614, 8,252,839, 8,536,363, 8,410,169, 8,232,316, 8,609,728, 8,350,079, 8,349,892, 7,999,007, 8,658,694, 8,653,137, 9,029,607, 8,765,813, 9,050,311, 9,199,908, 9,278,901, 8,747,897, 9,358,240, 9,339,507, 9,255,064, 9,278,902, 9,278,903, 9,758,465; 9,422,223; 9,878,972; 9,624,156; U.S. Published Patent Applications Nos. 2009-0036465, 2008-0200449, 2008-0280986, 2009-0124697, 2014-0275616, 2014-0275262, 2013-0184295, 2014-0323567, 2016-0030371, 2016-0051505, 2016-0030355, 2016-0143868, 2015-0328232, 2015-0148414, 2016-0045470, 2016-0129087, 2017-0095432; 2018-0153847 and PCT Publications Nos. WO00/57701, WO20160105538, WO2016038532, WO2018/058124.

A "prodrug" of treprostinil may refer to compounds which are converted in vivo to treprostinil or its pharmaceutically active derivatives thereof, or to a compound described in PCT publication No. WO2005/007081; U.S. Pat. Nos. 7,384,978, 7,417,070, 7,544,713, 8,252,839, 8,410,169, 8,536,363, 9,050,311, 9,199,908, 9,278,901, 9,422,223; 9,624,156, 9,878,972, 9,371,264, 9,394,227, 9,505,737, 9,758,465, 9,643,911, 9,701,616, 9,776,982, 9,845,305, 9,957,200, 10,494,327, 10,053,414, 10,246,403, 10,344, 012, 10,450,290, 10,464,877, 10,464,878, 10,703,706, 10,752,733, 9,255,064, 9,469,600, 10,010,518, 10,343,979, 10,526,274; U.S. Patent Application Publications Nos. 2018-0153847 and 2021-0054009; U.S. provisional patent application No. 63/036,561 filed Jun. 9, 2020; U.S. provisional patent application No. 63/125,145 filed Dec. 14, 2020, each of which is incorporated herein by reference in their entirety.

Prostacyclin is a small molecule that has been previously shown to cause dilation of large blood vessels, relaxation of smooth muscle, inhibition of smooth muscle proliferation, as well as inhibition of platelet aggregation, which is involved in the blood clotting process. Similar actions by treprostinil at the microvascular level and on capillaries near the skin are believed to help enhance cutaneous blood flow and heal and/or prevent ischemia lesions or ulcers associated with scleroderma, Buerger's disease, Raynaud's disease, Raynaud's phenomenon, and other conditions.

An "ester" of treprostinil may refer to a compound of formula:



wherein

R^1 is H, optionally substituted C_1-C_{10} alkyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted aryl, optionally substituted heteroaryl, or optionally substituted heterocyclyl;

R^2 and R^3 are each independently —C(O)R^4; and

each R^4 is independently optionally substituted C_1-C_{10} alkyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted aryl, optionally substituted heteroaryl, or optionally substituted heterocyclyl;

wherein at least one of R^1, R^2, and R^3, is not H.

"Optionally substituted" refers to a group selected from that group and a substituted form of that group. Substituents may include any of the groups defined below. In one embodiment, substituents are selected from C_1-C_{10} or C_1-C_6 alkyl, substituted C_1-C_{10} or C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_6-C_{10} aryl, C_3-C_5 cycloalkyl, C_2-C_{10} heterocyclyl, C_1-C_{10} heteroaryl, substituted C_2-C_6 alkenyl, substituted C_2-C_6 alkynyl, substituted C_6-C_{10} aryl, substituted C_3-C_8 cycloalkyl, substituted C_2-C_{10} heterocyclyl, substituted C_1-C_{10} heteroaryl, halo, nitro, cyano, —CO_2H or a C_1-C_6 alkyl ester thereof.

"Alkyl" refers to monovalent saturated aliphatic hydrocarbyl groups having from 1 to 10 carbon atoms and preferably 1 to 6 carbon atoms. This term includes, by way of example, linear and branched hydrocarbyl groups such as methyl (CH_3—), ethyl (CH_3CH_2—), n-propyl ($CH_3CH_2CH_2$—), isopropyl ((CH_3)$_2$CH—), n-butyl ($CH_3CH_2CH_2CH_2$—), isobutyl ((CH_3)$_2$$CHCH_2$—), sec-butyl (($CH_3$)($CH_3CH_2$)CH—), t-butyl (($CH_3$)$_3$C—), n-pentyl ($CH_3CH_2CH_2CH_2CH_2$), and neopentyl (($CH_3$)$_3$ CCH_2—).

"Alkenyl" refers to monovalent straight or branched hydrocarbyl groups having from 2 to 10 carbon atoms and preferably 2 to 6 carbon atoms or preferably 2 to 4 carbon atoms and having at least 1 and preferably from 1 to 2 sites of vinyl (>C═C<) unsaturation. Such groups are exemplified, for example, by vinyl, allyl, and but 3-en-1-yl. Included within this term are the cis and trans isomers or mixtures of these isomers.

"Alkynyl" refers to straight or branched monovalent hydrocarbyl groups having from 2 to 10 carbon atoms and preferably 2 to 6 carbon atoms or preferably 2 to 3 carbon atoms and having at least 1 and preferably from 1 to 2 sites of acetylenic (—C≡C—) unsaturation. Examples of such alkynyl groups include acetylenyl (—C≡CH), and propargyl (—CH_2C≡CH).

"Substituted alkyl" refers to an alkyl group having from 1 to 5, preferably 1 to 3, or more preferably 1 to 2 substituents selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, aryl, substituted aryl, aryloxy, substituted aryloxy, arylthio, substituted arylthio, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, cycloalkyl, substituted cycloalkyl, cycloalkyloxy, substituted cycloalkyloxy, cycloalkylthio, substituted cycloalkylthio, cycloalkenyl, substituted cycloalkenyl, cycloalkenyloxy, substituted cycloalkenyloxy, cycloalkenylthio, substituted cycloalkenylthio, guanidino, substituted guanidino, halo, hydroxy, heteroaryl, substituted heteroaryl, heteroaryloxy, substituted heteroaryloxy, heteroarylthio, substituted heteroarylthio, heterocyclic, substituted heterocyclic, heterocyclyloxy, substituted heterocyclyloxy, heterocyclylthio, substituted heterocyclylthio, nitro, SO_3H, substituted sulfonyl, substituted sulfonyloxy, thioacyl, thiol, alkylthio, and substituted alkylthio, wherein said substituents are as defined herein.

"Substituted alkenyl" refers to alkenyl groups having from 1 to 3 substituents, and preferably 1 to 2 substituents, selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, aryl, substituted aryl, aryloxy, substituted aryloxy, arylthio, substituted arylthio, carboxyl, carboxyl ester, (carboxyl ester) amino, (carboxyl ester)oxy, cyano, cycloalkyl, substituted cycloalkyl, cycloalkyloxy, substituted cycloalkyloxy, cycloalkylthio, substituted cycloalkylthio, cycloalkenyl, substituted cycloalkenyl, cycloalkenyloxy, substituted cycloalkenyloxy, cycloalkenylthio, substituted cycloalkenylthio, guanidino, substituted guanidino, halo, hydroxyl, heteroaryl, substituted heteroaryl, heteroaryloxy, substituted heteroaryloxy, heteroarylthio, substituted heteroarylthio, heterocyclic, substituted heterocyclic, heterocyclyloxy, substituted heterocyclyloxy, heterocyclylthio, substituted heterocyclylthio, nitro, SO_3H, substituted sulfonyl, substituted sulfonyloxy, thioacyl, thiol, alkylthio, and substituted alkylthio, wherein said substituents are as defined herein and with the proviso that any hydroxyl or thiol substitution is not attached to a vinyl (unsaturated) carbon atom.

"Substituted alkynyl" refers to alkynyl groups having from 1 to 3 substituents, and preferably 1 to 2 substituents, selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, aryl, substituted aryl, aryloxy, substituted aryloxy, arylthio, substituted arylthio, carboxyl, carboxyl ester, (carboxyl ester) amino, (carboxyl ester)oxy, cyano, cycloalkyl, substituted cycloalkyl, cycloalkyloxy, substituted cycloalkyloxy, cycloalkylthio, substituted cycloalkylthio, cycloalkenyl, substituted cycloalkenyl, cycloalkenyloxy, substituted cycloalkenyloxy, cycloalkenylthio, substituted cycloalkenylthio, guanidino, substituted guanidino, halo, hydroxy, heteroaryl, substituted heteroaryl, heteroaryloxy, substituted heteroaryloxy, heteroarylthio, substituted heteroarylthio, heterocyclic, substituted heterocyclic, heterocyclyloxy, sub-

stituted heterocyclyloxy, heterocyclylthio, substituted heterocyclylthio, nitro, SO_3H, substituted sulfonyl, substituted sulfonyloxy, thioacyl, thiol, alkylthio, and substituted alkylthio, wherein said substituents are as defined herein and with the proviso that any hydroxyl or thiol substitution is not attached to an acetylenic carbon atom.

"Alkoxy" refers to the group 0 alkyl wherein alkyl is defined herein. Alkoxy includes, by way of example, methoxy, ethoxy, n propoxy, isopropoxy, n butoxy, t butoxy, sec butoxy, and n pentoxy.

"Substituted alkoxy" refers to the group 0 (substituted alkyl) wherein substituted alkyl is defined herein.

"Acyl" refers to the groups H—C(O)—, alkyl-C(O)—, substituted alkyl-C(O)—, alkenyl-C(O)—, substituted alkenyl-C(O)—, alkynyl-C(O)—, substituted alkynyl-C(O)—, cycloalkyl-C(O)—, substituted cycloalkyl-C(O)—, cycloalkenyl-C(O)—, substituted cycloalkenyl-C(O)—, aryl-C(O)—, substituted aryl-C(O)—, heteroaryl-C(O)—, substituted heteroaryl-C(O)—, heterocyclic-C(O)—, and substituted heterocyclic-C(O)—, wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined herein. Acyl includes the "acetyl" group $CH_3C(O)$—.

"Acylamino" refers to the groups —$NR^{47}C(O)$alkyl, —$NR^{47}C(O)$substituted alkyl, —$NR^{47}C(O)$cycloalkyl, —$NR^{47}C(O)$substituted cycloalkyl, —$NR^{47}C(O)$cycloalkenyl, —$NR^{47}C(O)$substituted cycloalkenyl, —$NR^{47}C(O)$alkenyl, —$NR^{47}C(O)$substituted alkenyl, —$NR^{47}C(O)$alkynyl, —$NR^{47}C(O)$substituted alkynyl, —$NR^{47}C(O)$aryl, —$NR^{47}C(O)$substituted aryl, —$NR^{47}C(O)$heteroaryl, —$NR^{47}C(O)$substituted heteroaryl, —$NR^{47}C(O)$heterocyclic, and $NR^{47}C(O)$substituted heterocyclic wherein R^{47} is hydrogen or alkyl and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined herein.

"Acyloxy" refers to the groups alkyl-C(O)O—, substituted alkyl-C(O)O—, alkenyl-C(O)O—, substituted alkenyl-C(O)O—, alkynyl-C(O)O—, substituted alkynyl-C(O)O—, aryl-C(O)O—, substituted aryl-C(O)O—, cycloalkyl-C(O)O—, substituted cycloalkyl-C(O)O—, cycloalkenyl-C(O)O—, substituted cycloalkenyl-C(O)O—, heteroaryl-C(O)O—, substituted heteroaryl —C(O)O, heterocyclic-C(O)O—, and substituted heterocyclic-C(O)O— wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined herein.

"Amino" refers to the group NH_2.

"Substituted amino" refers to the group —$NR^{48}R^{49}$ where R^{48} and R^{49} are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, SO_2 alkyl, —SO_2-substituted alkyl, —SO_2-alkenyl, —SO_2-substituted alkenyl, —SO_2-cycloalkyl, —SO_2-substituted cycloalkyl, —SO_2-cycloalkenyl, —SO_2-substituted cylcoalkenyl, —SO_2-aryl, —SO_2-substituted aryl, —SO_2-heteroaryl, —SO_2-substituted heteroaryl, —SO_2-heterocyclic, and —SO_2-substituted heterocyclic and wherein R^{48} and R^{49} are optionally joined, together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group, provided that R^{48} and R^{49} are both not hydrogen, and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined herein. When R^{48} is hydrogen and R^{49} is alkyl, the substituted amino group is sometimes referred to herein as alkylamino. When R^{48} and R^{49} are alkyl, the substituted amino group is sometimes referred to herein as dialkylamino.

When referring to a monosubstituted amino, it is meant that either R^{48} or R^{49} is hydrogen but not both. When referring to a disubstituted amino, it is meant that neither R^{48} nor R^{49} are hydrogen.

"Pharmaceutically acceptable salt" may refer to physiologically acceptable salts of treprostinil, as well as non-physiologically acceptable salts of treprostinil. Pharmaceutically acceptable salts of compounds described herein are within the scope of the present technology and include acid or base addition salts which retain the desired pharmacological activity and is not biologically undesirable (e.g., the salt is not unduly toxic, allergenic, or irritating, and is bioavailable). When the compound of the present technology has a basic group, such as, for example, an amino group, pharmaceutically acceptable salts can be formed with inorganic acids (such as hydrochloric acid, hydroboric acid, nitric acid, sulfuric acid, and phosphoric acid), organic acids (e.g., alginate, formic acid, acetic acid, benzoic acid, gluconic acid, fumaric acid, oxalic acid, tartaric acid, lactic acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, naphthalene sulfonic acid, and p toluenesulfonic acid) or acidic amino acids (such as aspartic acid and glutamic acid). When the compound of the present technology (treprostinil, an ester, prodrug, or derivative thereof) has an acidic group, such as for example, a carboxylic acid group, it can form salts with metals, such as alkali and earth alkali metals (e.g., Na^+, Li^+, K^+, Ca^{2+}, Mg^{2+}, Zn^{2+}), ammonia or organic amines (e.g., dicyclohexylamine, trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, triethanolamine) or basic amino acids (e.g., arginine, lysine and ornithine). Such salts can be prepared in situ during isolation and purification of the compounds or by separately reacting the purified compound in its free base or free acid form with a suitable acid or base, respectively, and isolating the salt thus formed.

ILD may include a range of diseases and disorders, for example, idiopathic pulmonary fibrosis (IPF), desquamative interstitial pneumonia (DIP), acute interstitial pneumonia (AIP), nonspecific interstitial pneumonia (NSIP), respiratory bronchiolitis-associated interstitial lung disease (RB-ILD), cryptogenic organizing pneumonia (COP), lymphoid interstitial pneumonia (LIP), sarcoidosis, rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, polymyositis, dermatomyositis, antisynthetase syndrome, silicosis, asbestosis, occupational lung disease, chronic hypersensitivity pneumonitis, idiopathic interstitial pneumonia (IIP), an autoimmune ILD, lymphangioleiomyomatosis (LAM), Langerhans cell histiocytosis (LCH), drug associated ILD, vasculitis, granulomatosis, and berylliosis.

"Pulmonary function" as used herein, refers to the ability of the lungs to absorb oxygen and expand and contract. Pulmonary function, decline thereof, or reduction of the decline, may be assessed using medically recognized tools known to those having ordinary skill in the art. Methods

include pulmonary function testing (PFT), spirometry, lung volumes, maximal respiratory pressure, diffusing capacity, oxygen desaturation, and arterial blood gas evaluation.

"Forced vital capacity" as used herein, refers to the amount of air that can be forcibly exhaled from the lungs after taking the deepest breath possible, as measured by spirometry.

Further aspects of the present invention are concerned with the use of treprostinil or its derivatives, prodrugs, esters, or pharmaceutically acceptable salts thereof, in the manufacture of a medicament for the treatment or prevention of interstitial lung disease or a condition associated with interstitial lung disease. In some embodiments, the medicament is formulated for inhalation. When administered by inhalation, the formulation can be nebulized or formulated for a dry powder inhaler (DPI).

The amount of treprostinil or its derivative, or a pharmaceutically acceptable salt thereof, that is required in methods may depend on a number of factors, such as the specific indication it is being used for, the nature of the particular compound used, the mode of administration, the concentration, and the weight and condition of the subject. A daily dose per subject for ILD, or conditions associated with ILD may be in the range 25 μg to 250 mg or 7 μg to 285 μg, per day per kilogram bodyweight. In some embodiments, the daily dose may be in the range of about 150 μg to about 350 μg per day, about 200 μg to about 300 μg per day, or about 225 μg to about 275 μg per day. Intravenous doses in the range 0.5 μg to 1.5 mg per kilogram bodyweight per day may be administered as an infusion of from 0.5 ng to 1.0 μg per kilogram bodyweight per minute.

The treprostinil or its derivative, prodrug, ester, or a pharmaceutically acceptable salt thereof, can be administered using any suitable treatment schedule. In some embodiments, the drug will be administered multiple times a day (1, 2, 3, 4, or 5), and in other embodiments, the drug can be continuously administered, such as by using an infusion pump. The duration of treatment can vary depending on the severity of disease, treatment goals, or individual circumstances. In some embodiments, the duration of treatment is at least one week, at least two weeks, at least four weeks, at least eight weeks, or at least sixteen weeks. In some embodiments, the duration of treatment is indefinite, e.g., treatment can continue for the life of the subject or until disease symptoms decrease below some threshold.

Pharmaceutical compositions described herein or administered to subjects, hereinafter referred to as a "formulation" or "composition," of treprostinil and/or its prodrugs, esters, derivatives, and/or pharmaceutically acceptable salts thereof, may be admixed with, inter alia, an acceptable carrier. The carrier may be compatible with any other ingredients in the formulation and not deleterious to the subject. The carrier may be a solid or a liquid, or both. One or more of treprostinil or its derivatives, esters, prodrugs, or pharmaceutically acceptable salts thereof, may be incorporated in the formulations of the invention. Formulations administered include those suitable for parenteral, oral, inhalation, rectal, topical, buccal and transdermal administration.

Parenterally administered compositions may be isotonic with the blood of the intended recipient. Subcutaneous injection, intravenous, intramuscular or intradermal injection may be used. Such preparations may conveniently be prepared by admixing the compound with water or a glycine or citrate buffer and rendering the resulting solution sterile and isotonic with the blood.

Formulations suitable for oral administration may be presented as capsules, cachets, lozenges, or tablets, each containing a specific amount of treprostinil or its derivative, prodrug, ester, or a pharmaceutically acceptable salt thereof; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water or water-in-oil emulsion. Oral formulations that may be administered include those described in U.S. Pat. Nos. 7,384,978 and 8,747,897 (including the commercial product Orenitram® (treprostinil) Extended-Release Tablets), the entire disclosures of which are hereby incorporated by reference. In general, the formulations of the invention are prepared by uniformly and intimately admixing treprostinil, an ester, prodrug, or salt thereof with a liquid or finely divided solid carrier, or both, and then, if necessary, shaping the resulting mixture.

Formulations suitable for buccal (sub-lingual) administration include lozenges comprising treprostinil or its derivative, prodrug, ester, or a pharmaceutically acceptable salt thereof, in a flavored base, usually sucrose and acacia or tragacanth; and pastilles comprising the compound in an inert base such as gelatin and glycerin or sucrose and acacia.

Formulations suitable for rectal administration are preferably presented as unit dose suppositories. These may be prepared by admixing treprostinil or its derivative, prodrug, ester, or a pharmaceutically acceptable salt thereof, with one or more solid carriers.

Topical and transdermal formulations me be an ointment, cream, lotion, paste, gel, spray, aerosol, or oil. Carriers possible include vaseline, lanoline, polyethylene glycols, alcohols, and combinations thereof.

Treprostinil, prodrugs, esters, and salts thereof are conveniently prepared by methods the same as or analogous to those described in U.S. Pat. Nos. 4,306,075, 6,528,688 and 6,441,245, the disclosures of which are hereby incorporated by reference.

In some embodiments of the present methods, the treprostinil administered is provided as a kit with instructions for use in treating ILD. In certain kit embodiments, the treprostinil or its derivative, prodrug, ester, or a pharmaceutically acceptable salt thereof, is in a form suitable for subcutaneous administration, continuous subcutaneous infusion, intravenously administration or inhalation. Subcutaneous formulations administered to the subject may include any of those described in U.S. Pat. No. 7,999,007 (including the commercial product Remodulin® (treprostinil) Injection), the entire disclosure of which is hereby incorporated by reference. In other kit embodiments, the treprostinil or its derivative, or a pharmaceutically acceptable salt thereof, is in an orally available form selected from the group consisting of tablets and capsules.

The effects of the method on pulmonary fibroses (PF) can be ascertained via an animal model of PF such as bleomycin and vanadium pentoxide (V205) models as described in Bonner J C, Rice A B, Ingram J L, Moomaw C R, Nyska A, Bradbury A, Sessoms A R, Chulada P C, Morgan D L, Zeldin D C, and Langenbach R. Susceptibility of cyclooxygenase-2-deficient mice to pulmonary fibrogenesis. *Am J Pathol* 161: 459-470, 2002; 23; and Keerthisingam C B, Jenkins R G, Harrison N K, Hernandez-Rodriguez N A, Booth H, Laurent G J, Hart S L, Foster M L, and McAnulty R J. Cyclooxygenase-2 deficiency results in a loss of the anti-proliferative response to transforming growth 31 factor-beta in human fibrotic lung fibroblasts and promotes bleomycin-induced pulmonary fibrosis in mice. *Am J Pathol* 158: 1411-1422, 2001, incorporated herein by reference in their entirety.

In preferred embodiments, treprostinil is administered via inhalation. Inhaled compositions comprising treprostinil may include sprays, aerosols, and dry powder compositions. Said compositions may include a variety of excipients. Inhalable compositions administered may include any of those described in U.S. Pat. No. 9,339,507 (including the commercial product Tyvaso® (treprostinil) Inhalation Solution), WO2017192993 and WO2014085813, the entire disclosures of which are hereby incorporated by reference.

The excipient or excipients of the pharmaceutical composition according to the invention may have water solubility greater than 5 g/l and often greater than 100 g/l and more. They are preferably chosen among sugars, salts or amino acids and have double function of minimizing the effect of the inhaled composition on the fluid's cellular outcome. Regarding the composition in its solid dry form, the excipient also forms the solid matrix in which the treprostinil, a prodrug, ester, salt, or derivative thereof is dispersed.

The composition may include excipients such as lactose, corn starch, or the like, glidants such as magnesium stearate, etc., emulsifying agents, suspending agents, stabilizers, and isotonic agents, etc. If desired, a sweetening agent and/or a flavoring agent may be added. Exemplary excipients include, without limitation, polyethylene glycol (PEG), hydrogenated castor oil (HCO), cremophors, carbohydrates, starches (e.g., corn starch), inorganic salts, antimicrobial agents, antioxidants, binders/fillers, surfactants, lubricants (e.g., calcium or magnesium stearate), glidants such as talc, disintegrants, diluents, buffers, acids, bases, film coats, combinations thereof, and the like. Other examples of soluble excipients that may be used in the composition according to the invention are alitame, acesulfame potassium, aspartame, saccharin, sodium saccharin, sodium cyclamate, sucralose, threalose, xylitol, citric acid, tartaric acid, cyclodextrins, dextrins, hydroxyethylcellulose, gelatine, malic acid, maltitol, maltodextrin, maltose, polydextrose, tartaric acid, sodium or potassium bicarbonate, sodium or potassium chloride, sodium or potassium citrate, phospholipids, lactose, sucrose, glucose, fructose, mannitol, sorbitol, natural aminoacids, alanine, glycine, serine, cysteine, phenylalanine, tyrosine, tryptophan, histidine, methionine, threonine, valine, isoleucine, leucine, arginine, lysine, aspartic acid, glutamic acid, asparagine, glutamine, proline, their salts, and their possible simple chemical modifications such as in N-acetylcysteine, and carbocysteine.

The preferred soluble excipients are alkaline metals salts such as sodium chloride or potassium chloride, and sugars, such as lactose. Specific carbohydrate excipients include, for example, monosaccharides, such as fructose, maltose, galactose, glucose, D-mannose, sorbose, and the like; disaccharides, such as lactose, sucrose, trehalose, cellobiose, and the like; polysaccharides, such as raffinose, melezitose, maltodextrins, dextrans, starches, and the like; and alditols, such as mannitol, xylitol, maltitol, lactitol, xylitol, sorbitol (glucitol), pyranosyl sorbitol, myoinositol, and the like.

As far as the hollow morphology of the particles of the dry powder is concerned, the composition requires the presence of a soluble excipient, preferably a sugar like lactose, able to form in the beginning of the solvent evaporation phase during preparation of the composition, during spray-drying, the backbone of the particle, producing high porosity particles.

In some embodiments, the excipient comprises a surfactant. The surfactant of the composition can be chosen among different classes of surfactants of pharmaceutical use.

Surfactants suitable to be used in the present invention are all those substances characterized by medium or low molecular weight that contain a hydrophobic moiety, generally readily soluble in an organic solvent but weakly soluble or insoluble in water, and a hydrophilic (or polar) moiety, weakly soluble or insoluble in an organic solvent but readily soluble in water. Surfactants are classified according to their polar moiety. Therefore, surfactant with a negatively charged polar moiety are called anionic surfactants, while cationic surfactants have a positively charged polar moiety. Uncharged surfactant are generally called non-ionic, while surfactant charged both positively and negatively are called zwitterionic. Examples of anionic surfactants are salts of fatty acids (better known as soaps), sulfates, sulfate ethers and phosphate esters. Cationic surfactants are frequently based on polar groups containing amino groups. Most common non-ionic surfactants are based on polar groups containing oligo-(ethylene-oxide) groups. Zwitterionic surfactants are generally characterized by a polar group formed by a quaternary amine and a sulfuric or carboxylic group.

Specific examples of this application are the following surfactants: benzalkonium chloride, cetrimide, docusate sodium, glyceryl monolaurate, sorbitan esters, sodium lauryl sulfate, polysorbates, phospholipids, biliary salts.

Non-ionic surfactants, such as polysorbates and polyethylene and polyoxypropylene block copolymers, known as "Poloxamers," may be used. Polysorbates are described in the CTFA International Cosmetic Ingredient Dictionary as mixtures of sorbitol and sorbitol anhydride fatty acid esters condensed with ethylene oxide. Particularly preferred are non-ionic surfactants of the series known as "Tween," in particular the surfactant known as "Tween 80," a polyoxyethylensorbitan. Additional exemplary excipients include surfactants such as other polysorbates, e.g., "Tween 20" and pluronics such as F68 and F88 (both of which are available from BASF, Mount Olive, N.J.), sorbitan esters, lipids (e.g., phospholipids such as lecithin and other phosphatidylcholines, and phosphatidylethanolamines), fatty acids and fatty esters, steroids such as cholesterol, and chelating agents, such as EDTA, zinc and other such suitable cations.

The presence of a surfactant, and preferably of Tween 80, may be necessary to reduce electrostatic charges found in compositions without it, the flow of the powder and the maintenance of the solid state in a homogeneous way without initial crystallization. According to the present invention, phospholipids are included in the above-mentioned definition of surfactants or excipients.

The inhalatory formulation according administered can include a hydrophobic substance in order to reduce sensitivity to humidity. Such hydrophobic substance is preferably leucine, which makes the particle disaggregation easier.

In case of production of a solid product in powder form, this can occur using different techniques, well consolidated in the pharmaceutical industry. The preparation of fine particles through spray-drying represents a preferred method according to the invention. In case of industrial production, this technique is undoubtedly preferred to freeze-drying, which at the moment is the most expensive drying process, both for the apparatus used, and for the yield and production times.

The pharmaceutical composition according to the invention can include other components, such as pH buffers and preservatives. Buffers include, but are not limited to, citric acid, sodium chloride, potassium chloride, sodium sulfate, potassium nitrate, sodium phosphate monobasic, sodium phosphate dibasic, and combinations thereof.

Further, a composition administered may optionally include one or more acids or bases. Non-limiting examples of acids that can be used include those acids selected from

the group consisting of hydrochloric acid, acetic acid, phosphoric acid, citric acid, malic acid, lactic acid, formic acid, trichloroacetic acid, nitric acid, perchloric acid, phosphoric acid, sulfuric acid, fumaric acid, and combinations thereof. Non-limiting examples of suitable bases include bases selected from the group consisting of sodium hydroxide, sodium acetate, ammonium hydroxide, potassium hydroxide, ammonium acetate, potassium acetate, sodium phosphate, potassium phosphate, sodium citrate, sodium formate, sodium sulfate, potassium sulfate, potassium fumerate, and combinations thereof.

The excipients may include an antioxidant, for example, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, hypophosphorous acid, monothioglycerol, propyl gallate, sodium bisulfite, sodium formaldehyde sulfoxylate, sodium metabisulfite, and combinations thereof.

The term "dry powder" in reference to the composition of the invention, refers to a powder, granulate, tablet form composition, or any other solid form with a humidity content that assures to the composition chemical stability in time. More precisely, the term "dry" refers to a solid composition with water content lower than 10% w/w, normally less than 5% and preferably less than 3%.

The amount of any excipient in the dry powder composition of the invention can change within a wide range. The amount of any individual excipient in the composition will vary depending on the role of the excipient, the dosage requirements of the active agent components, and particular needs of the composition. Generally, however, the excipient will be present in the composition in an amount of about 1% to about 99% by weight, preferably from about 5% to about 98% by weight, more preferably from about 15% to about 95% by weight of the excipient. In general, the amount of excipient present in a composition of the disclosure is selected from the following: at least about 2%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or even 95% by weight.

The treprostinil composition administered may be provided as a kit that includes a metered dose inhaler containing a pharmaceutical composition comprising treprostinil or its derivative, ester, prodrug, or a pharmaceutically acceptable salt thereof. Such a kit can further include instructions on how to use the metered dose inhaler for inhaling treprostinil. Such instructions can include, for example, information on how to coordinate patient's breathing, and actuation of the inhaler. The kit can be used by a subject, such as human being, affected with ILD that can be treated by treprostinil. In some cases, the kit is a kit for treating ILD, that includes (i) a metered dose inhaler containing a pharmaceutical composition comprising treprostinil or its derivative, ester, prodrug, or a pharmaceutically acceptable salt thereof; and (ii) instructions for use of the metered dose inhaler containing treprostinil in treating pulmonary hypertension.

The present disclosure also provides a method of treating a pulmonary hypertension due to a condition selected from a chronic lung disease and/or hypoxia (low oxygen levels) by administering to a subject, such as a human being, with such the pulmonary hypertension an effective amount of treprostinil, its prodrug, its pharmaceutically acceptable salt or a pharmaceutically acceptable salt of its prodrug. Pulmonary hypertension due to a chronic lung disease and/or hypoxia belongs Group 3 pulmonary hypertension according to the World Health Organization (WHO) classification.

The chronic lung disease may include an obstructive lung disease in which the lung airways are narrow and make it difficult to exhale, such as chronic obstructive pulmonary disease (COPD) and emphysema; a restrictive lung disease in which the lungs have a difficult time expanding when one inhales, such as interstitial lung disease or pulmonary fibrosis; sleep apnea; living in an area of high altitude for a long period of time; and various combinations of the above conditions.

In some embodiments, the chronic lung disease may include idiopathic interstitial pneumonia, such as idiopathic pulmonary fibrosis, idiopathic nonspecific interstitial pneumonia, respiratory bronchiolitis (e.g. respiratory bronchiolitis associated with interstitial lung disease), desquamative interstitial pneumonia, acute interstitial pneumonia; chronic hypersensitivity pneumonitis, occupational lung disease, pulmonary fibrosis, emphysema, connective tissue disease or any combination of the above conditions.

In some embodiments, administering the effective amount of treprostinil, its prodrug, its pharmaceutically acceptable salt or a pharmaceutically acceptable salt of its prodrug may provide an increase, which may be statistically significant, in a six minute walk distance (6MWD) in a subject with a pulmonary hypertension due to a condition selected from a chronic lung disease and/or hypoxia compared to a baseline 6MWD value, i.e. a 6MWD value prior to the administering. For example, the 6MWD value may be statistically significantly increased after at least 4 weeks, at least 5 weeks, at least 6 weeks, at least 7 weeks, at least 8 weeks, at least 9 weeks, at least 10 weeks, at least 11 weeks, at least 12 weeks, at least 13 weeks, at least 14 weeks, at least 15 weeks or at least 16 weeks or at least 20 weeks or at least 24 weeks or at least 28 weeks or at least 32 weeks or at least 36 weeks or at least 40 weeks or at least 44 weeks or at least 48 weeks or at least 52 weeks of the administering. In some embodiments, the administering may provide an increase of at least 5 m, at least 10 m or at least 15 m in the 6MWD compared to the baseline 6MWD value after at least 8 weeks, at least 9 weeks, at least 10 weeks, at least 11 weeks, at least 12 weeks, at least 13 weeks, at least 14 weeks, at least 15 weeks or at least 16 weeks or at least 20 weeks or at least 24 weeks or at least 28 weeks or at least 32 weeks or at least 36 weeks or at least 40 weeks or at least 44 weeks or at least 48 weeks or at least 52 weeks of the administering. In some embodiments, the administering may provide an increase of at least 5 m, at least 10 m, at least 15 m, at least 18 m or at least 20 m in the 6MWD compared to the baseline 6MWD value after at least 12 weeks, at least 13 weeks, at least 14 weeks, at least 15 weeks or at least 16 weeks of the administering.

In some embodiments, administering the effective amount of treprostinil, its prodrug, its pharmaceutically acceptable salt or a pharmaceutically acceptable salt of its prodrug may provide an reduction, which may be statistically significant, in a plasma concentration of NT-proBNP in a subject with a pulmonary hypertension due to a condition selected from a chronic lung disease and/or hypoxia compared to a baseline NT-proBNP plasma concentration, i.e. a NT-proBNP plasma concentration value prior to the administering. For example, the NT-proBNP plasma concentration may be statistically significantly reduced after at least 4 weeks, at least 5 weeks, at least 6 weeks, at least 7 weeks, at least 8 weeks, at least 9 weeks, at least 10 weeks, at least 11 weeks, at least 12 weeks, at least 13 weeks, at least 14 weeks, at least 15 weeks or at least 16 weeks or at least 20 weeks or at least 24 weeks or at least 28 weeks or at least 32 weeks or at least 36 weeks or at least 40 weeks or at least 44 weeks or at least 48 weeks or at least 52 weeks of the administering. In some embodiments, the administering may provide a reduction of at least 50 pg/ml, at least 100 pg/ml, at least 150 pg/ml, at least 200 pg/ml, at least 250 pg/ml, at least 300 pg/ml or at least 350 pg/ml in the NT-proBNP plasma concentration compared to

the baseline the NT-proBNP plasma concentration value after at least 8 weeks, at least 9 weeks, at least 10 weeks, at least 11 weeks, at least 12 weeks, at least 13 weeks, at least 14 weeks, at least 15 weeks or at least 16 weeks of the administering.

In some embodiments, administering the effective amount of treprostinil, its prodrug, its pharmaceutically acceptable salt or a pharmaceutically acceptable salt of its prodrug to a subject with a pulmonary hypertension due to a chronic lung disease may provide a reduction, which may be statistically significant, of a number of exacerbation(s) of the chronic lung disease. For example, a number of exacerbation(s) of the chronic lung disease may be lower in a patient subpopulation with the pulmonary hypertension due to the chronic lung disease, who was administered the effective amount of treprostinil, its prodrug, its pharmaceutically acceptable salt or a pharmaceutically acceptable salt of its prodrug for at least 4 weeks, at least 5 weeks, at least 6 weeks, at least 7 weeks, at least 8 weeks, at least 9 weeks, at least 10 weeks, at least 11 weeks, at least 12 weeks, at least 13 weeks, at least 14 weeks, at least 15 weeks or at least 16 weeks or at least 20 weeks or at least 24 weeks or at least 28 weeks or at least 32 weeks or at least 36 weeks or at least 40 weeks or at least 44 weeks or at least 48 weeks or at least 52 weeks, compared to a patient subpopulation with the same condition, which was administered a placebo instead of treprostinil. For example, the number of exacerbation(s) may be lowered by at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70% or at least 80%. The exacerbation(s) may include an acute, clinically significant, respiratory deterioration characterized by evidence of new widespread alveolar abnormality.

In some embodiments, administering the effective amount of treprostinil, its prodrug, its pharmaceutically acceptable salt or a pharmaceutically acceptable salt of its prodrug to a subject with a pulmonary hypertension due to a chronic lung disease and/or hypoxia may provide a reduction, which may be statistically significant, of a number of clinical worsening event(s). For example, a number of clinical worsening event(s) may be lower in a patient subpopulation with the pulmonary hypertension due to the chronic lung disease and/or hypoxia, who was administered the effective amount of treprostinil, its prodrug, its pharmaceutically acceptable salt or a pharmaceutically acceptable salt of its prodrug for at least 4 weeks, at least 5 weeks, at least 6 weeks, at least 7 weeks, at least 8 weeks, at least 9 weeks, at least 10 weeks, at least 11 weeks, at least 12 weeks, at least 13 weeks, at least 14 weeks, at least 15 weeks or at least 16 weeks or at least 20 weeks or at least 24 weeks or at least 28 weeks or at least 32 weeks or at least 36 weeks or at least 40 weeks or at least 44 weeks or at least 48 weeks or at least 52 weeks compared to a patient subpopulation with the same condition, which was administered a placebo instead of treprostinil. For example, the number of clinical worsening event(s) may be lowered by at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70% or at least 80%. The clinical worsening event(s) may include one or more of hospitalization due to a cardiopulmonary indication, a decrease in a 6MWD by more than 15% from a baseline 6MWD value, death or a lung transplantation.

In some embodiments, administering the effective amount of treprostinil, its prodrug, its pharmaceutically acceptable salt or a pharmaceutically acceptable salt of its prodrug may provide an improvement, which may be statistically significant, in forced vital capacity (FVC) in a subject with a pulmonary hypertension due to a condition selected from a chronic lung disease and/or hypoxia. For example, the FVC may be higher in a patient subpopulation with the pulmonary hypertension due to the chronic lung disease and/or hypoxia, who was administered the effective amount of treprostinil, its prodrug, its pharmaceutically acceptable salt or a pharmaceutically acceptable salt of its prodrug for at least 4 weeks, at least 5 weeks, at least 6 weeks, at least 7 weeks, at least 8 weeks, at least 9 weeks, at least 10 weeks, at least 11 weeks, at least 12 weeks, at least 13 weeks, at least 14 weeks, at least 15 weeks or at least 16 weeks, or at least 20 weeks or at least 24 weeks or at least 28 weeks or at least 32 weeks or at least 36 weeks or at least 40 weeks or at least 44 weeks or at least 48 weeks or at least 52 weeks, compared to a patient subpopulation with the same condition, which was administered a placebo instead of treprostinil. For example, the FVC value may be higher by at least 10 ml or at least 15 ml or at least 20 ml or at least 25 ml or at least 30 ml or at least 35 ml or at least 40 ml or at least 45 ml after at least 4 weeks, at least 5 weeks, at least 6 weeks, at least 7 weeks, at least 8 weeks, at least 9 weeks, at least 10 weeks, at least 11 weeks, at least 12 weeks, at least 13 weeks, at least 14 weeks, at least 15 weeks or at least 16 weeks of the administering in the patient subpopulation with the pulmonary hypertension due to the chronic lung disease and/or hypoxia, who was administered the effective amount of treprostinil, its prodrug, its pharmaceutically acceptable salt or a pharmaceutically acceptable salt of its prodrug compared to the patient subpopulation with the same condition, which was administered a placebo instead of treprostinil. In patients with a chronic lung disease, such as interstitial lung disease, and/or hypoxia, an FVC value usually decreases with time when untreated. Thus, administering the effective amount of treprostinil, its prodrug, its pharmaceutically acceptable salt or a pharmaceutically acceptable salt may increase an FVC value compared to an FVC value before the administering; maintain an FVC value within 5%, 10% or 20% within the FVC value prior to the administering; or reduce a decrease of an FVC value with time compared to a decrease in an FVC value with no administering the effective amount of treprostinil, its prodrug, its pharmaceutically acceptable salt or a pharmaceutically acceptable salt, such a decrease in an FVC value when placebo is administered instead of treprostinil, its prodrug, its pharmaceutically acceptable salt or a pharmaceutically acceptable salt.

In some embodiments, treprostinil, its prodrug, its pharmaceutically acceptable salt or a pharmaceutically acceptable salt of its prodrug may be administered by inhalation, which may be, for example, an oral inhalation or a nasal inhalation. In some embodiments, treprostinil, its prodrug, its pharmaceutically acceptable salt or a pharmaceutically acceptable salt of its prodrug may be administered by an inhalation device, which may be for example, a pulsed inhalation device, such as a metered dose inhaler and/or a pulsed nebulizer. Pulsed inhalation devices are disclosed, for example, in U.S. patent application publication No. 20080200449, U.S. Pat. Nos. 9,358,240; 9,339,507; 10,376,525; and 10,716,793, each of which is incorporated herein by reference in its entirety.

In some embodiments, the inhalation device, such as a pulsed inhalation device, may contain a solution or a suspension comprising treprostinil, its prodrug, its pharmaceutically acceptable salt or a pharmaceutically acceptable salt of its prodrug. For example, such solution or suspension may be used for aerosolizing or a nebulizing by an inhalation device, such as a nebulizer and/or a metered dose inhaler. One example of a solution may be a commercial product Tyvaso®. A concentration of treprostinil in such solution may vary. In some embodiments, the treprostinil concentra-

tion may be from 200 μg/ml to 2000 μg/ml or from 300 μg/ml to 1500 μg/ml or from 400 μg/ml to 1200 μg/ml or any value or subrange within these ranges. For example, in a certain embodiment, the treprostinil concentration may be 600 μg/ml.

In some embodiments, the inhalation device, such as a pulsed inhalation device, may be a dry powder inhaler, which may contain a dry powder composition or formulation comprising treprostinil, its prodrug, its pharmaceutically acceptable salt or a pharmaceutically acceptable salt of its prodrug. For example, a dry powder inhaler and a dry powder composition or formulation comprising treprostinil are disclosed in WO2019/237028, which incorporated herein by reference in its entirety. In some embodiments, in addition to treprostinil, its prodrug, its pharmaceutically acceptable salt or a pharmaceutically acceptable salt of its prodrug, the dry powder composition may further a diketopiperazine, such as (E)-3,6-bis[4-(N-carbonyl-2-propenyl) amidobutyl]-2,5-diketopiperazine (FDKP).

Treprostinil, its prodrug, its pharmaceutically acceptable salt or a pharmaceutically acceptable salt of its prodrug may be administered by inhalation in a single administering event which may involve a limited number of breaths (or inhalations) by the subject. For example, in some embodiments, a number of breaths in the single administering event may not exceed 20 breaths (or inhalations) or 19 breaths (or inhalations) or 18 breaths (or inhalations) or 17 breaths (or inhalations) or 16 breaths (or inhalations) or 15 breaths (or inhalations) or 14 breaths (or inhalations) or 13 breaths (or inhalations) or 12 breaths (or inhalations) or 11 breaths (or inhalations) or 10 breaths (or inhalations) or 9 breaths (or breaths (or inhalations) inhalations) or 8 breaths (or inhalations) or 7 breaths (or inhalations) or 6 breaths (or inhalations) or 5 breaths (or inhalations) or 4 breaths (or inhalations) or 3 breaths (or inhalations) or 2 breaths (or inhalations) or 1 breath (or inhalation).

A dose of treprostinil, its prodrug, its pharmaceutically acceptable salt or a pharmaceutically acceptable salt of its prodrug administered by inhalation in a single administering event may vary. In some embodiments, the single administering event dose may be from 7.5 μg to 100 μg or 10 μg to 100 μg or 15 μg to 100 μg from 15 μg to 90 μg or from 15 μg to 75 μg or from 30 μg to 75 μg or any value or subrange within these ranges.

A number of single administering events per day for administering treprostinil, its prodrug, its pharmaceutically acceptable salt or a pharmaceutically acceptable salt of its prodrug administered by inhalation may vary. For example, the number of single administering events per day may be 1, 2, 3, 4, 5 or 6 per day.

The table below provides exemplary doses of treprostinil in a dry powder formulation, which may be used in a dry powder inhaler, and how they may compare with treprostinil doses in Tyvaso® inhalation solution.

DPI (treprostinil) Inhalation Powder Cartridge Strength (QID)	Tyvaso (treprostinil) Inhalation Solution Number of Breaths (QID)
16 mcg	2 to 4 (18 to 24 mcg)
32 mcg	5 to 7 (30 to 42 mcg)
48 mcg	8 to 10 (48 to 60 mcg)
64 mcg	11 to 13 (66 to 78 mcg)

The disclosure of all publications cited above are expressly incorporated herein by reference in their entireties to the same extent as if each were incorporated by reference individually.

The examples described herein are illustrative of the present invention and are not intended to be limitations thereon. Different embodiments of the present invention have been described according to the present invention. Many modifications and variations may be made to the techniques described and illustrated herein without departing from the spirit and scope of the invention. Accordingly, it should be understood that the examples are illustrative only and are not limiting upon the scope of the invention.

EXAMPLES

Example 1: Inhaled Treprostinil Results on Underlying Lung Disease

An exacerbation of underlying lung disease is defined as an acute, clinically significant, respiratory deterioration characterized by evidence of new widespread alveolar abnormality (Collard et al., 2016). The present example shows that treatment with inhaled treprostinil resulted in significantly fewer exacerbations of underlying lung disease in patients.

Subjects having underlying lung disease were treated with inhaled treprostinil over 16 weeks. Subjects initiated inhaled treprostinil or placebo at a dose of 3 breaths (18 mcg) 4 times daily (during waking hours). Study drug doses were maximized throughout the study. Dose escalations (additional 1 breath 4 times daily) could occur up to every 3 days with a target dosing regimen of 9 breaths (54 mcg) 4 times daily and a maximum dose of 12 breaths (72 mcg) 4 times daily, as clinically tolerated. Subjects were assessed during Screening and Baseline to determine eligibility for the study. Once eligible, 5 Treatment Phase visits to the clinic were required at Week 4, Week 8, Week 12, Week 15, and Week 16 (final study visit). An Early Termination (ET) Visit was conducted for subjects who discontinued prior to Week 16; all assessments planned for the final Week 16 Visit were conducted during the ET Visit, if applicable. Subjects were contacted at least weekly by telephone or email to assess tolerance to study drug, adverse events (AEs), and changes to concomitant medications.

Efficacy assessments consisted of 6MWD, plasma NT-proBNP concentration, and time to clinical worsening. Exploratory endpoints included SGRQ, change in DSP, time to exacerbation of underlying disease, and pulmonary function tests. Safety assessments consisted of the development of AEs, vital signs, clinical laboratory parameters, ECG parameters, hospitalizations due to cardiopulmonary indications, exacerbations of underlying lung disease, and oxygenation.

Treatment resulted in significantly fewer exacerbations of underlying lung disease over the 16-week treatment period (26.4% in Inhaled Treprostinil group and 38.7% in placebo group; p=0.018) and decreased risk of an exacerbation of underlying lung disease (hazard ratio 0.66 or 34% reduction in risk) as shown in FIG. **1**.

In addition, the following FVC suggestive data was obtained from this study. Among patients treated with inhaled treprostinil, overall results from intent to treat group were:

Overall ITT
- 28.47 mL and 44.40 mL in FVC at Weeks 8 and 16
- Percent predicted FVC at Week 8 (1.79%; p=0.0139) and Week 16 (1.80%; p=0.0277).
- Subset IIP etiology:
  - 46.48 mL and 108.18 mL (p=0.0229) at Weeks 8 and 16
  - Percent predicted FVC at Week 8 (1.95%, p=0.0373) and Week 16 (2.88%; p=0.0096)
- Subset IPF etiology:
  - 84.52 mL and 168.52 mL (p=0.0108) at Weeks 8 and 16
  - Percent predicted FVC at Week 8 (2.54%; p=0.0380) and Week 16 (3.50%; p=0.0147)

Nintedanib: IPF~109 mL (3.2% predicted) at 52 weeks
Pirfenidone: IPF~153-193 mL at 52 weeks

Placebo corrected, rate of decline (not improvements)

In comparison to the known treatments for ILD (nintedanib and pirfenidone) shown above, inhaled treprostinil achieves comparable effects with shorter treatment duration.

Pulmonary function testing was initially conducted as a safety assessment (Safety Population) during the study. The results indicated that although most PFT parameters remained stable for subjects in the study, a notable improvement in FVC (% predicted) was observed at Week 16 in the inhaled treprostinil group (median improvement of 1.0% compared to a 1.0% reduction in the placebo group). As a result, post hoc MMRM analyses of FVC data were performed for the ITT Population and are presented in Table 1 (ITT Population), Table 2 (by PH ILD Etiology of IIP) and Table 3 (for subjects with IPF), shown below.

TABLE 1

Analysis of FVC Data Using Mixed Model Repeated Measurement - ITT Population

Visit	Treatment	N	LS Mean	Contrast	Estimated Difference	95% CI	p-value
				FVC (mL)			
Week 8	Inhaled treprostinil	142	5.49	Inhaled treprostinil – Placebo	28.47	−30.81, 87.74	0.3453
	Placebo	141	−22.98				
Week 16	Inhaled treprostinil	130	9.77	Inhaled treprostinil – Placebo	44.40	−25.25, 114.05	0.2106
	Placebo	126	−34.63				
				FVC (% predicted)			
Week 8	Inhaled treprostinil	142	0.77	Inhaled treprostinil – Placebo	1.79	0.37, 3.21	0.0139
	Placebo	141	−1.02				
Week 16	Inhaled treprostinil	130	1.07	Inhaled treprostinil – Placebo	1.80	0.20, 3.39	0.0277
	Placebo	126	−0.72				

Abbreviations:

CI, confidence interval;

FVC, forced vital capacity;

ITT, Intent-to-Treat;

LS, least square;

MMRM, mixed model repeated measurement

LSMean, p-values, estimated difference, and associated 95% CI were from the MMRM with the change from baseline in FVC/% predicted FVC as the dependent variable; treatment, week, treatment by week interaction as the fixed effects; baseline FVC/% predicted FVC as the covariate; and subject as the random effect. An unstructured variance/covariance structure shared across treatment groups was used to model the within-subject errors.

TABLE 2

Analysis of FVC Data Using Mixed Model Repeated Measurement for PH-ILD Etiology of IIP - ITT Population

Visit	Treatment	N	LS Mean	Contrast	Estimated Difference	95% CI	p-value
				PH-ILD Etiology: IIP FVC (mL)			
Week 8	Inhaled treprostinil	58	9.27	Inhaled treprostinil – Placebo	46.48	−32.55, 125.51	0.2467
	Placebo	71	−37.21				
Week 16	Inhaled treprostinil	52	22.16	Inhaled treprostinil – Placebo	108.18	15.25, 201.10	0.0229
	Placebo	63	−86.02				
				FVC (% predicted)			
Week 8	Inhaled treprostinil	58	0.92	Inhaled treprostinil – Placebo	1.95	0.12, 3.79	0.0373
	Placebo	71	−1.03				
Week 16	Inhaled treprostinil	52	1.66	Inhaled treprostinil – Placebo	2.88	0.72, 5.05	0.0096
	Placebo	63	−1.23				

Abbreviations:

CI, confidence interval;

CPFE, combined pulmonary fibrosis and emphysema;

CTD, connective tissue disease;

FVC, forced vital capacity;

ILD, interstitial lung disease;

IIP, idiopathic interstitial pneumonia;

ITT, Intent-to-Treat;

LS, least square;

MMRM, mixed model repeated measurement

LSMean, p-values, estimated difference, and associated 95% CI were from the MMRM with the change from baseline in FVC/% predicted FVC as the dependent variable; treatment, week, treatment by week interaction as the fixed effects; baseline FVC/% predicted FVC as the covariate; and subject as the random effect. An unstructured variance/covariance structure shared across treatment groups was used to model the within-subject errors.

Table 3: Analysis of FVC Data Using Mixed Model Repeated Measurement for Subjects with IPF - ITT for IIP Subjects

IPF							
FVC (mL)							
Week 8	Inhaled treprostinil	31	41.69	Inhaled treprostinil - Placebo	84.522	−20.409, 189.454	0.1128
	Placebo	47	−42.83				
Week 16	Inhaled treprostinil	28	38.24	Inhaled treprostinil - Placebo	168.524	40.078, 296.970	0.0108
	Placebo	42	−130.3				
FVC (% predicted)							
Week 8	Inhaled treprostinil	31	1.60	Inhaled treprostinil - Placebo	2.543	0.145, 4.941	0.0380
	Placebo	47	−0.94				
Week 16	Inhaled treprostinil	28	1.62	Inhaled treprostinil - Placebo	3.504	0.712, 6.295	0.0147
	Placebo	42	−1.88				

Abbreviations:
CI, confidence interval;
FVC, forced vital capacity;
IPF, idiopathic pulmonary fibrosis;
ITT, Intent-to-Treat;
LS, least square; MMRM, mixed model repeated measurement
LSMean, p-values, estimated difference, and associated 95% CI were from the MMRM with the change from baseline in FVC/% predicted FVC as the dependent variable; treatment, week, treatment by week interaction as the fixed effects; baseline FVC/% predicted FVC as the covariate; and subject as the random effect. An unstructured variance/covariance structure shared across treatment groups was used to model the within-subject errors.

Treatment with inhaled treprostinil resulted in improvements of 28.47 mL and 44.40 mL in FVC at Weeks 8 and 16, respectively; significant when presented as % predicted FVC at Week 8 (1.79%; p=0.0139) and Week 16 (1.80%; p=0.0277).

When FVC was analyzed by PH-ILD etiology of IIP, treatment with inhaled treprostinil resulted in improvements of 46.48 mL and 108.18 mL (p=0.0229) when compared to placebo at Weeks 8 and 16, respectively. The between group differences for % predicted FVC were statistically significant at Week 8 (1.95%, p=0.0373) and Week 16 (2.88%; p=0.0096).

Further analysis of FVC for subjects with an IPF etiology (using only the IIP subjects in the ITT Population), showed that treatment with inhaled treprostinil resulted in improvements of 84.52 mL and 168.52 mL (p=0.0108) compared to placebo at Weeks 8 and 16, respectively. The between group differences for % predicted FVC were statistically significant at Week 8 (2.54%; p=0.0380) and Week 16 (3.50%; p=0.0147).

Example 2

The following prophetic example will assess efficacy of treprostinil as indicated for the treatment of chronic fibrosing interstitial lung diseases (CF-ILDs) including Idiopathic Interstitial Pneumonias (IIPs) including IPF, chronic hypersensitivity pneumonitis (CHP), and environmental/occupational fibrosing lung disease.

Patients may be treated with inhaled treprostinil up to 15 breaths QID based upon tolerability. Change from baseline to Week 24 of treatment in FVC (absolute or percent predicted) as primary efficacy endpoint will be assessed. Parameters that may be assessed include time to exacerbation of underlying lung disease, 6 meter walk distance test (6MWD), all-cause mortality/survival, time to death, additional analyses of FVC (e.g. absolute and relative change), changes from baseline in SpO_2, diffusing capacity of the lungs for carbon monoxide (DLCO), NT-proBNP, and King's Brief Interstitial Lung Disease Questionnaire.

REFERENCES

1. Collard et al., *American Journal of Respiratory and Critical Care Medicine*, Volume 194 Number 3, pg. 265.

2. Meyer et al., (Apr. 3, 2017). *Therapeutics and Clinical Risk Management*. 13: 427-437.

Example 3: Inhaled Treprostinil in Pulmonary Hypertension Due to Interstitial Lung Disease

No therapies are currently approved for the treatment of pulmonary hypertension in patients with interstitial lung disease. The safety and efficacy of inhaled treprostinil for patients with this condition are unclear.

Methods

We enrolled patients with interstitial lung disease and pulmonary hypertension (documented by right heart catheterization) in a multicenter, randomized, double-blind, placebo-controlled, 16-week trial. Patients were assigned in a 1:1 ratio to receive inhaled treprostinil, administered by means of an ultrasonic, pulsed-delivery nebulizer in up to 12 breaths (total, 72 μg) four times daily, or placebo. The primary efficacy end point was the difference between the two treatment groups in the change in peak 6-minute walk distance from baseline to week 16. Secondary end points included the change in N-terminal pro-B-type natriuretic peptide (NT-proBNP) level at week 16 and the time to clinical worsening.

Results

A total of 326 patients underwent randomization, with 163 assigned to inhaled treprostinil and 163 to placebo. Baseline characteristics were similar in the two groups. At week 16, the least-squares mean difference between the treprostinil group and the placebo group in the change from baseline in the 6-minute walk distance was 31.12 m (95% confidence interval [CI], 16.85 to 45.39; P<0.001). There was a reduction of 15% in NT-proBNP levels from baseline with inhaled treprostinil as compared with an increase of 46% with placebo (treatment ratio, 0.58; 95% CI, 0.47 to 0.72; P<0.001). Clinical worsening occurred in 37 patients (22.7%) in the treprostinil group as compared with 54 patients (33.1%) in the placebo group (hazard ratio, 0.61;

95% CI, 0.40 to 0.92; P=0.04 by the log-rank test). The most frequently reported adverse events were cough, headache, dyspnea, dizziness, nausea, fatigue, and diarrhea.

Conclusions

In patients with pulmonary hypertension due to interstitial lung disease, inhaled treprostinil improved exercise capacity from baseline, assessed with the use of a 6-minute walk test, as compared with placebo.

Precapillary pulmonary hypertension is defined as an elevation in mean pulmonary arterial pressure and pulmonary vascular resistance.[1] In the World Health Organization (WHO) classification of pulmonary hypertension, precapillary pulmonary hypertension due to lung disease is classified as group 3. The most common lung diseases associated with group 3 pulmonary hypertension are chronic obstructive pulmonary disease and interstitial lung disease.

Pulmonary hypertension has been reported in up to 86% of patients with interstitial lung disease and is associated with reduced exercise capacity, greater need for supplemental oxygen, decreased quality of life, and earlier death.[2-4] Despite the global prevalence and poor clinical course of pulmonary hypertension due to interstitial lung disease, there are currently no approved therapies for these patients. Although data are limited, therapies approved for group 1 pulmonary hyper-tension (pulmonary arterial hypertension) have been used to treat group 3 pulmonary hypertension.[5] Previous studies of vasodilator therapies have shown conflicting results. The largest trial to date evaluated the soluble guanylate cyclase stimulator riociguat in a patient population with group 3 pulmonary hypertension and was stopped early owing to serious harm.[6] Treprostinil is a stable analogue of prostacyclin, which promotes direct vasodilation of pulmonary and systemic arterial vascular beds and inhibits platelet aggregation.[7] An inhaled formulation of treprostinil was previously shown to improve exercise capacity after 12 weeks of therapy in patients with group 1 pulmonary hypertension.[8] Data from previously completed pilot studies suggest that inhaled treprostinil can improve hemodynamics and functional capacity in patients with group 3 pulmonary hypertension.[9-12] Therefore, the objective of the INCREASE trial was to evaluate the safety and efficacy of inhaled treprostinil in patients with pulmonary hypertension due to interstitial lung disease.

Trial Design and Oversight

INCREASE was a multicenter, randomized, double-blind, placebo-controlled trial. The trial was monitored by an independent data and safety monitoring committee and was conducted in accordance with Good Clinical Practice guidelines.

Trial Population

The trial population consisted of patients 18 years of age or older in whom interstitial lung disease was diagnosed on the basis of evidence of diffuse parenchymal lung disease on computed tomography of the chest (not centrally adjudicated) performed within 6 months before randomization. Confirmation of group 3 pulmonary hypertension by right heart catheterization within 1 year before randomization was required. Group 3 pulmonary hypertension was defined by pulmonary vascular resistance of more than 3 Wood units, pulmonary capillary wedge pressure of 15 mm Hg or lower, and mean pulmonary arterial pressure of 25 mm Hg or higher. Patients with group 3 pulmonary hypertension due to connective tissue disease were also required to have a baseline forced vital capacity of less than 70%. Eligible patients also had to walk at least 100 m during a 6-minute walk test. Patients receiving drug treatment (i.e., pirfenidone or nintedanib) for their underlying lung disease were required to have been receiving a stable dose for at least 30 days before undergoing randomization. Patients receiving approved therapy for pulmonary arterial hypertension within 60 days before randomization were not eligible for enrollment. Written informed consent was obtained from all the patients.

TABLE 4

Characteristics of the Patients at Baseline.*

Characteristic	Inhaled Treprostinil (N = 163)	Placebo (N = 163)	All Patients (N = 326)
Female sex - no. (%)	85 (52.1)	68 (41.7)	153 (46.9)
Mean age at randomization (range) - yr	65.6 (26-90)	67.4 (36-85)	66.5 (26-90)
Age distribution - no. (%)			
<65 yr	64 (39.3)	48 (29.4)	112 (34.4)
65 to <80 yr	83 (50.9)	100 (61.3)	183 (56.1)
≥80 yr	16 (9.8)	15 (9.2)	31 (9.5)
Race or ethnic group - no. (%)†			
White	112 (68.7)	126 (77.3)	238 (73.0)
Black or African American	41 (25.2)	30 (18.4)	71 (21.8)
American Indian or Alaska Native	2 (1.2)	1 (0.6)	3 (0.9)
Asian	7 (4.3	5 (3.1)	12 (3.7)
Multiple	0	1 (0.6)	1 (0.3)
Unknown	1 (0.6)	0	1 (0.03)
Hispanic or Latino ethnic group - no. (%)†			
Yes	11 (6.7)	16 (9.8)	27 (8.3)
No	152 (93.3)	146 (89.6)	298 (91.4)
Data missing	0	1 (0.6)	1 (0.3)
Mean time since diagnosis - yr	0.54 ± 1.16	0.54 ± 1.31	0.54 ± 1.23

TABLE 4-continued

Characteristics of the Patients at Baseline.*

Characteristic	Inhaled Treprostinil (N = 163)	Placebo (N = 163)	All Patients (N = 326)
Cause of lung disease - no. (%)			
Idiopathic interstitial pneumonia	65 (39.9)	81 (49.7)	146 (44.8)
Chronic hypersensitivity pneumonitis	10 (6.1)	9 (5.5)	19 (5.8)
Occupational lung disease	5 (3.1)	1 (0.6)	6 (1.8)
Combined pulmonary fibrosis and emphysema	42 (25.8)	40 (24.5)	82 (25.2)
Connective tissue disease	40 (24.5)	32 (19.6)	72 (22.1)
Other	1 (0.6)	0	1 (0.3)
Idiopathic interstitial pneumonia subcategory - no. (%)			
Idiopathic pulmonary fibrosis	37 (22.7)	55 (33.7)	92 (28.2)
Idiopathic nonspecific interstitial pneumonia	21 (12.9)	16 (9.8)	37 (11.3)
Respiratory bronchiolitis associated with interstitial lung disease	2 (1.2)	0	2 (0.6)
Desquamative interstitial pneumonia	0	1 (0.6)	1 (0.3)
Acute interstitial pneumonia	0	1 (0.6)	1 (0.3)
Unclassified idiopathic interstitial pneumonia	5 (3.1)	8 (4.9)	13 (4.0)
Use of supplemental oxygen - no. (%)	119 (73.0)	114 (69.9)	233 (71.5)
Background therapy - no (%)			
None	133 (81.6)	119 (73.0)	252 (77.3)
Pirfenidone only	19 (11.7)	25 (15.3)	44 (13.5)
Nintedanib only	11 (6.7)	19 (11.7)	30 (9.2)

*Plus-minus values are means ± SD. Additional patient characteristics at baseline are provided in Table S2 in the Supplementary Appendix. Percentages may not total 100 because of rounding.
†Race and ethnic group were reported by the patient.

Trial Procedures

Within 30 days after screening, eligible patients were randomly assigned in a 1:1 ratio to receive inhaled treprostinil (Tyvaso, United Therapeutics) or placebo in a double-blind manner. Randomization, based on permuted blocks, was stratified by baseline 6-minute walk distance (≤350 m vs. >350 m) and was implemented through an interactive Web-response system.

Inhaled treprostinil (0.6 mg per milliliter) was administered by means of an ultrasonic, pulsed-delivery nebulizer at 6 μg per breath. Placebo was administered similarly as a visually identical solution. The first dose of trial drug (3 breaths) was administered in the clinic, followed by at least a 1-hour observation period. The dose of treprostinil or placebo was adjusted, with dose escalation (an additional 1 breath four times daily) occurring as often as every 3 days, with a target dose of 9 breaths four times daily and a maxi-mum dose of 12 breaths four times daily. Investigators adjusted the dose on an individual patient basis to achieve the maximum tolerated dose leading to functional improvement.

Trial Assessments

The 6-minute walk test was performed and laboratory data were obtained at baseline and at weeks 4, 8, 12, and 16, or at the time of early discontinuation of treprostinil or placebo. Each 6-minute walk test was performed 10 to 60 minutes after the most recent dose of active drug or placebo, which is the time of peak plasma treprostinil exposure. A trough test was performed at week 15 at least 4 hours after the participant received a dose of treprostinil or placebo and at least 24 hours before the week 16 test. Pulse oximetry was performed immediately before, during, and after each 6-minute walk test. Measurement of N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels and pulmonary function tests were performed at baseline and at weeks 8 and 16 (or at early discontinuation) after the patients recovered from the 6-minute walk test. The St. George's Respiratory Questionnaire (SGRQ), a quality-of-life measure, was completed at baseline and week 16 or at the time of early discontinuation.

Outcome Measures

The primary end point of the trial was the difference between the two groups in the change in peak 6-minute walk distance from baseline to week 16. Secondary efficacy end points were analyzed in the following hierarchical testing order: the change in NT-proBNP level from baseline to week 16, the time to clinical worsening, the change in 6-minute walk distance at peak plasma treprostinil level at week 12, and the change in 6-minute walk distance at trough treprostinil level at week 15. The time to clinical worsening was evaluated from the time of randomization until the patient's withdrawal from the trial and was defined as the time until the occurrence of any one of the following events: hospitalization for a cardiopulmonary indication, a decrease in 6-minute walk distance greater than 15% from baseline that was directly related to the disease under study at two consecutive visits and at least 24 hours apart, death from any cause, or lung transplantation.

Exploratory end points were the changes in peak 6-minute walk distance at weeks 4 and 8, quality of life as measured with the use of the SGRQ at week 16, and the distance-saturation product (calculated by multiplying the total distance walked by the lowest oxygen saturation measurement during the 6-minute walk) at week 16. Safety end points included adverse events, abnormal laboratory results, oxy-

genation as measured by pulse oximetry (Spo2) and supplemental oxygen requirement, changes in pulmonary function test results, hospitalization for a cardiopulmonary indication, and investigator-reported exacerbations of underlying lung disease, defined as acute, clinically significant respiratory deterioration characterized by evidence of new widespread alveolar abnormality.

Statistical Analysis

Original estimates suggested that with 266 patients randomly assigned in a 1:1 ratio to receive inhaled treprostinil or placebo, the trial would have at least 90% power at a significance level of 0.05 (two-sided) to detect a between-group difference of 30 m in the change in peak 6-minute walk distance from baseline at week 16, assuming a standard deviation of 75 m. To account for approximately 15% of participants discontinuing the trial, 314 patients would need to be enrolled.

For the primary efficacy analysis, the change in 6-minute walk distance was analyzed by mixed-model repeated-measures methods, under the assumption that missing data were missing at random. The model included the change from baseline to peak 6-minute walk distance as the dependent variable, with treatment, week, and treatment-by-week interaction as fixed effects, and the baseline 6-minute walk distance as a covariate. A sensitivity analysis for the primary end point was performed by means of a multiple imputation approach with a multivariate normal imputation model according to the Markov chain Monte Carlo method. The imputation model included treatment group, all scheduled visits, the patient's sex, and the patient's age at randomization. If the result for the primary efficacy end point was significant, secondary efficacy end points were to be evaluated according to a hierarchical testing procedure. Confidence intervals have not been adjusted for multiplicity and cannot be used to infer definitive treatment effects for secondary efficacy end points.

Results

Patients

Of 462 patients screened for eligibility, 326 were enrolled at 93 centers and were randomly assigned to receive placebo (163 patients) or inhaled treprostinil (163 patients) (FIG. **2**). Baseline characteristics were similar in the two groups (Table 4). The mean age of the patients was 66.5 years, 46.9% were female, and the most common diagnosis was idiopathic interstitial pneumonia (in 44.8%). At baseline, the mean 6-minute walk distance was 259.6 m, the mean pulmonary vascular resistance was 6.2 Wood units, and the mean NT-proBNP level was 1832.9 pg per milliliter.

Exposure and Follow-up

Patients in the treprostinil group took a median of 11 breaths from the inhaler (66 μg) at each of four daily sessions at week 12 and 12 breaths (72 μg) per session at week 16. The percentage of patients in this group who took 10 to 12 breaths (60 to 72 μg) per session was 57.0% at week 12 and 57.8% at week 16. Patients in the placebo group took a median of 12 breaths from the inhaler per session at weeks 12 and 16.

Forty patients assigned to receive inhaled treprostinil (24.5%) and 38 assigned to placebo (23.3%) discontinued the assigned regimen pre-maturely. These patients were encouraged to remain in the trial and complete assessments through week 16; 33 patients in the treprostinil group and 35 in the placebo group discontinued participation in the trial. The reasons for discontinuation are shown in FIG. **2**.

Primary End Point

Mean within-group changes in the 6-minute walk distance are shown in FIG. **2**. Mixed-model repeated-measures analysis showed that the least-squares mean difference between the treprostinil group and the placebo group in the change from baseline in peak 6-minute walk distance was 31.12 m (95% confidence interval [CI], 16.85 to 45.39; P<0.001) (Table 5 and FIG. **4**). Similar effects were observed across subgroups, including subgroups defined by disease cause and severity (as measured by baseline 6-minute walk distance), baseline hemodynamics, and dose group (FIG. **5**). In addition, the between-group difference in the change from baseline in peak 6-minute walk distance at week 16 was significant when analyzed with multiple imputation according to the Markov chain Monte Carlo method (30.97 m; 95% CI, 16.53 to 45.41; P<0.001) (FIG. **6**).

TABLE 5

Summary of Primary and Secondary End Points.*

End Point	Inhaled Treprostinil (N = 163)	Placebo (N = 163)	Treatment Effect (95% CI)	P Value
Primary end point				
Change in peak 6-minute walk distance from baseline to wk 16 - m†	21.08 ± 5.12	−10.04 ± 5.12	31.12 ± 7.25 (16.85 to 45.39)‡	<0.001
Secondary end points§				
Change in plasma concentration of NT-proBNP from baseline to wk 16¶				
Mean (±SD) change - pg/ml	−396.35 ± 1904.90	1453.95 ± 7296.20		
Median - pg/ml	−22.65	20.65		
Range - pg/ml	−11,433.0 to 5373.1	−5483.3 to 87,148.3		
Ratio to baseline	0.85 ± 0.06	1.46 ± 0.11	±0.58 ± 0.06 (0.47 to 0.72)‖	<0.001

TABLE 5-continued

Summary of Primary and Secondary End Points.*

End Point	Inhaled Treprostinil (N = 163)	Placebo (N = 163)	Treatment Effect (95% CI)	P Value
Occurrence of clinical worsening - no. (%)			0.61 (0.4 to 0.92)**	0.04
Any event	37 (22.7)	54 (33.1)		
Hospitalization for cardiopulmonary indication	18 (11.0)	24 (14.7)		
Decrease in 6 minute walk distance of >15% from baseline	13 (8.0)	26 (16.0)		
Death from any cause	4 (2.5)	4 (2.5)		
Lung transplantation	2 (1.2)	0		
Least-squares mean change in peak 6- minute walk distance from baseline to wk 12 - m†	18.77 ± 4.99	−12.52 ± 5.01	31.29 ± 7.07 (17.37 to 45.21)‡	<0.001
Least-squares mean change in trough 6- minute walk distance from baseline to wk 15 - m	9.3 ± 5.5	−12.7 ± 5.5	21.99 ± 7.7± (6.85 to 37.14)†	0.005††

*Plus-minus values are means ± SE, unless otherwise indicated. For secondary end points, the confidence intervals (CIs) have not been adjusted for multiplicity and cannot be used to infer definitive treatment effects. NT-proBNP denotes N-terminal pro-B-type natriuretic peptide.
†The effect of inhaled treprostinil as compared with placebo on the change in 6-minute walk distance was evaluated with the use of a mixed-model repeat measurement with the change from baseline in peak 6-minute walk distance as the dependent variable; treatment, week, and treatment-by-week interaction as the fixed effects; baseline 6-minute walk distance as the covariate; and subject as the random effect. Results are shown in Figures S1 and S3.
‡This is a least-squares mean difference between the groups.
§The effect of inhaled treprostinil as compared with placebo on the change in log-transformed NT-proBNP was evaluated with the use of a mixed-model repeat measurement with the change from baseline in log-transformed NT-proBNP as the dependent variable; treatment, week, and treatment-by-week interaction as the fixed effects; and log-transformed baseline NT-proBNP as the covariate. Ratio to baseline is the least-squares mean of the change from baseline in log-transformed data.
¶The change in plasma concentration of NT-proBNP from baseline to week 16 was assessed in 156 patients in the treprostinil group and 160 in the placebo group.
||This is the treatment ratio, which is the ratio of ratios between two treatment groups.
**This is a hazard ratio, calculated from a Cox proportional-hazards model. The P value was calculated with the use of a log-rank test stratified by the baseline 6-minute walk distance category.
††The P value was obtained from 100 multiple imputations with Markov chain Monte Carlo estimation with the use of analysis of covariance (ANCOVA) modeling, with the change from baseline in peak 6-minute walk distance as the dependent variable, treatment as a fixed effect, and baseline 6-minute walk distance as a covariate.

Secondary and Exploratory End Points

Patients assigned to inhaled treprostinil, as compared with those assigned to placebo, showed significant improvements in each of the secondary end points (Table 5). The NT-proBNP level decreased 15% from baseline with inhaled treprostinil and increased 46% from baseline with placebo, as assessed by the least-squares mean for the log-transformed ratio to the baseline level at week 16 (treatment ratio, 0.58; 95% CI, 0.47 to 0.72; P<0.001) (FIG. **7**). Clinical worsening occurred in 37 patients (22.7%) in the treprostinil group, as compared with 54 patients (33.1%) in the placebo group (hazard ratio, 0.61; 95% CI, 0.40 to 0.92; P=0.04 by the log-rank test) (FIG. **1**). The least-squares mean change from baseline to week 12 in peak 6-minute walk distance was 31.29 m greater in the treprostinil group than in the placebo group (P<0.001), and the change from baseline to week 15 in trough 6-minute walk distance was 21.99 m greater in the treprostinil group (P=0.004). There was no significant between-group difference in patient-reported quality of life as assessed with the SGRQ or in the distance-saturation product at week 16.

Safety End Points

TABLE 6

Summary of Adverse Events

Variable	Inhaled Treprostinil (N = 163)	Placebo (N = 163)	P Value*
Total no. of adverse events	890	793	
Patients with ≥1 adverse event - no. (%)	152 (93.3)	149 (91.4)	0.68
Total no. of serious adverse events†	53	89	
Patients with ≥1 serious adverse event - no. (%)	38 (23.3)	42 (25.8)	0.70
Total no. of adverse events leading to withdrawal of treprostinil or placebo	47	38	
Most frequently occurring adverse events - no. of patients (%)‡			
Cough	71 (43.6)	54 (33.1)	0.07
Headache	45 (27.6)	32 (19.6)	0.12
Dyspnea	41 (25.2)	51 (31.3)	0.27
Dizziness	30 (18.4)	23 (14.1)	0.37
Nausea	25 (15.3)	26 (16.0)	>0.99

TABLE 6-continued

Summary of Adverse Events

Variable	Inhaled Treprostinil (N = 163)	Placebo (N = 163)	P Value*
Fatigue	23 (14.1)	23 (14.1)	>0.99
Diarrhea	22 (13.5)	19 (11.7)	0.74
Throat irritation	20 (12.3)	6 (3.7)	0.007
Oropharyngeal pain	18 (11.0)	4 (2.5)	0.003
NT-proBNP increased	9 (5.5)	25 (15.3)	0.006

*P values were calculated with the use of Fisher's exact test.

‡Shown are the most frequently occurring adverse events occurring in more than 10% of patients in either group in the safety population, which comprised all patients who underwent randomization and received at least one dose of treprostinil or placebo.

The most frequently reported adverse events were cough, headache, dyspnea, dizziness, nausea, fatigue, and diarrhea (Table 6). Most of these events were of mild-to-moderate intensity.

Serious adverse events occurred in 23.3% of the patients who received inhaled treprostinil and in 25.8% of those who received placebo. No serious adverse events were reported significantly more frequently in the treprostinil group than in the placebo group.

Significantly fewer patients in the treprostinil group than in the placebo group had exacerbations of underlying lung disease (43 [26.4%] vs. 63 [38.7%]; P=0.02 by Fisher's exact test). Fewer patients in the treprostinil group than in the placebo group had a first occurrence of clinical worsening that involved hospitalization for a cardiopulmonary indication (18 [11.0%] vs. 24 [14.7%]; P=0.41). Inhaled treprostinil had no deleterious effect on any pulmonary function test variable during the trial. There were no significant treatment-related changes in pulse oximetry or supplemental oxygen use in either group over the trial period.

Discussion

Pulmonary hypertension frequently complicates the treatment of patients with interstitial lung disease and is associated with worse functional status, greater need for supplemental oxygen, and worse outcomes.[3, 13] In the INCREASE trial, patients treated with inhaled treprostinil had significant improvements in exercise capacity, as evidenced by changes in the 6-minute walk distance. Treatment with inhaled treprostinil was also associated with a lower risk of clinical worsening than that in patients who received placebo, as well as reductions in NT-proBNP levels and fewer exacerbations of underlying lung disease, over the 16-week treatment period. The safety profile of inhaled treprostinil observed in this vulnerable patient population was similar to that reported in previous studies. The most frequently reported adverse events were cough, headache, dyspnea, dizziness, nausea, fatigue, and diarrhea. The use of inhaled treprostinil was not associated with any decrement in lung function.

Patients with group 3 pulmonary hypertension are often treated with systemic pulmonary vasodilators, which are currently approved only for treatment of group 1 pulmonary hypertension. However, there is concern that such agents could worsen ventilation-perfusion matching in patients with group 3 pulmonary hypertension. Inhaled agents have the advantage of preferentially redirecting blood flow to the best-ventilated lung units, thus reducing the risk of ventilation-perfusion mismatching.[9, 14] Indeed, a retrospective study of inhaled treprostinil in patients with group 3 pulmonary hypertension showed that such patients had improvements in functional class and 6-minute walk distance without any adverse effect on peripheral oxygen saturation, rein-forcing the concept of unchanged or even improved ventilation-perfusion matching with inhaled treprostinil.[10] Similarly, in the current trial, we found no evidence of worsened oxygenation, which further allays concerns about ventilation-perfusion mismatching.

The INCREASE trial was not without its limitations. The trial was of short duration, and 21% of the patients discontinued the trial prematurely (before week 16). In addition, events of clinical worsening and exacerbation of underlying lung disease were investigator-reported and not adjudicated by an independent review committee. Finally, the size of the favorable treatment effect on the 6-minute walk distance with inhaled treprostinil is similar to estimates of the minimum clinically important difference for this test in patients with pulmonary disease (21.7 to 37 m in a study by Nathan et al., and 24 to 45 m in a study by du Bois et al.).[15, 16]

This study showed that among patients with pulmonary hypertension due to interstitial lung disease, treatment with inhaled treprostinil improved exercise capacity as shown by improvement in the 6-minute walk distance through the end of the 16-week treatment period. In addition, treatment with inhaled treprostinil was associated with a lower risk of clinical worsening than that with placebo, a reduction in NT-proBNP levels, and fewer exacerbations of underlying lung disease.

Supplemental Information

TABLE 7

Additional Baseline Patient Characteristics.

	Inhaled Treprostinil (N = 163)	Placebo (N = 163)	All Patients (N = 326)
6-minute walk distance, meters; mean (range) Median	254.1 (100-538) 256.0	265.1 (30-505) 260.0	259.6 (30-538) 259.0
Pulmonary vascular resistance, Woods units; mean (range) Median	6.369 (3.11-8.05) 5.570	6.013 (3.06-17.62) 5.060	6.191 (3.06-18.05) 5.275
NT-proBNP, pg/mL; mean (range)	1857.53 (10.2-21942.0)	1808.86 (23.0-16297.0)	1832.88 (10.2-21942.0)

TABLE 7-continued

Additional Baseline Patient Characteristics.

	Inhaled Treprostinil (N = 163)	Placebo (N = 163)	All Patients (N = 326)
Median*	550.50	420.80	503.85
Pulmonary arterial pressure, mmHg; mean (range	37.2 (25-74)	36.0 (25-61)	36.6 (25-74)
Median	35.0	35.0	35.0
Pulmonary capillary wedge pressure, mmHg; mean (range)	10.1 (2-20)	9.6 (0-15)	9.8 (0-20)
Median	10.0	10.0	10.0
Pulmonary function tests			
FEV1% Predicted; mean (range)	63.9 (23, 120)	65.0 (22, 145)	
Median	63.0	63.0	
FVC % Predicted; mean (range)	62.5 (24, 130)	63.8 (20, 134)	
Median	60.0	61.0	
TLC % Predicted; mean (range)	62.9 (25, 126)	64.2 (30, 109)	
Median	62.0	62.5	
DLCO % Predicted; mean (range)	30.0 (5, 86)	28.1 (1, 86)	
Median	29.0	26.0	

DLCO, lung diffusion capacity;
FEV1, forced expiratory volume in 1 second;
FVC, forced vital capacity;
NT-proBNP, N-terminal pro-brain natriuretic peptide;
TLC, total lung capacity
*N = 156 inhaled treprostinil; N = 160 placebo

TABLE 8

St. George's Respiratory Questionnaire Results.

	Inhaled Treprostinil N = 163		Placebo N = 163	
Visit Statistic	Value	Change from Baseline	Value	Change from Baseline
Baseline				
n	143		134	
Mean (SD)	57.17 (15.77)		57.67 (15.78)	
Median	59.80		56.30	
Interquartile	45.60, 67.90		46.50 70.70	
Min, Max	14.7, 94.9		18.4 88.6	
Week 16				
n	143	143	134	134
Mean (SD)	55.91 (17.07)	−1.25 (10.99)	57.49 (15.33)	−0.18 (10.72)
Median	56.30	−0.70	55.50	0.10
Interquartile	40.50, 67.00	−7.10, 5.20	46.80 69.70	−6.50, 6.10
Min, Max	3.5, 92.0	−40.4, 29.0	16.9 96.5	−31.9, 33.3
LS Mean (SE)		−1.30 (0.87)		−0.13 (0.90)
LS Mean Difference (SE) and (95% CI)		−1.18, (1.25) (−3.63, 1.28)		

ANCOVA, analysis of covariance;
CI, confidence interval;
LS Mean, least squares mean;
SD, standard deviation;
SE, standard error

The St. George's Respiratory Questionnaire has a range of results from 0 to 100, with higher scores indicating greater impairment and with a minimum clinically important difference of 4 points.

The changes from baseline in Total Score and each of the 3 domain scores were analyzed by parametric ANCOVA with no imputation for missing data.

The confidence intervals have not been adjusted for multiplicity and cannot be used to infer definitive treatment effects.

TABLE S4

Distance Saturation Product Results by Study Visit (m %).

Visit/Variable Statistic	Inhaled Treprostinil N = 163	Placebo N = 163
Baseline		
n	118	109
Mean (SD)	208.140 (81.130)	218.247 (77.405)
Median	201.320	215.760
Interquartile	150.060, 256.750	170.800, 268.800
Min, Max	77.04, 421.07	63.00, 417.35
Week 16 Change from Baseline		
n	118	109
Mean (SD)	7.607 (45.680)	−4.803 (53.026)
Median	8.385	−1.950
Interquartile	−12.960, 34.890	−38.180, 32.000
Min, Max	−217.26, 117.42	−184.85, 129.28
LS Mean (SE)	7.2 (4.5)	−4.3 (4.7)
LS Mean Difference (SE) and 95% CI	11.51 (6.5), 95% CI (−1.33, 24.35)	

ANCOVA, analysis of covariance;
CI, confidence interval;
LS Mean, least squares mean;
SD, standard deviation;
SE, standard error;
SpO_2, saturation of peripheral capillary oxygenation

Change in distance saturation product is the product of distance walked and lowest SpO_2 recorded during the 6-minute walk test.[7] Change from baseline to Week 16 in distance saturation product was analyzed by parametric ANCOVA with no imputation for missing distance saturation product values.

The confidence intervals have not been adjusted for multiplicity and cannot be used to infer definitive treatment effects.

TABLE 9

Serious Adverse Events by Preferred Term

Serious Adverse Events	Inhaled treprostinil N = 163 n	Placebo N = 163 n
Any Serious Event	53 events in 38 patients (23.3%)	89 events in 42 patients (25.8%)
Acute respiratory failure	4	5
Death with unknown cause	3	1
Dyspnoea	3	7
Interstitial lung disease	3	2
Bronchitis	2	1
Chronic obstructive pulmonary disease	2	2
Chronic respiratory failure	2	0
Respiratory failure	2	5
Upper respiratory tract infection	2	1
Acute myocardial infarction	1	2
Acute right ventricular failure	1	0

TABLE 9-continued

Serious Adverse Events by Preferred Term

Serious Adverse Events	Inhaled treprostinil N = 163 n	Placebo N = 163 n
Arrhythmia	1	0
B-cell lymphoma	1	0
Bronchopulmonary aspergillosis	1	0
Cardiac arrest	1	2
Cardiac failure congestive	1	2
Cardiopulmonary failure	1	0
Cellulitis	1	0
Cerebral haemorrhage	1	0
Chest pain	1	1
Combined pulmonary fibrosis and emphysema	1	0
Cor pulmonale	1	0
Haemoptysis	1	0
Hyperglycaemia	1	0
Hypervolaemia	1	0
Hypoxia	1	0
Idiopathic pulmonary fibrosis	1	4
Influenza	1	1
Left ventricular failure	1	0
Pain in extremity	1	0
Pneumonia	1	9
Pneumothorax	1	1
Pulmonary hypertension	1	1
Pulmonary oedema	1	0
Rhinovirus infection	1	0
Right ventricular failure	1	2
Syncope	1	1
Tachycardia	1	0
Abdominal pain	0	2
Acute kidney injury	0	1
Aspiration	0	1
Atrial fibrillation	0	1
Bradycardia	0	1
Cardiac failure	0	2
Cardiac failure acute	0	1
Cardiogenic shock	0	1
Chronic right ventricular failure	0	1
Coagulopathy	0	1
Cor pulmonale acute	0	1
Coronary artery disease	0	1
Disease progression	0	2
Epistaxis	0	1
Fluid overload	0	4
Haematochezia	0	1
Hypertension	0	1
Lumbar vertebral fracture	0	1
Metabolic encephalopathy	0	1
Pain	0	1
Pneumonia influenzal	0	1
Post procedural infection	0	1
Presyncope	0	2
Pulmonary congestion	0	1
Respiratory distress	0	1
Scleroderma	0	1
Sepsis	0	2
Transplant dysfunction	0	1
Urosepsis	0	1

TABLE 10

Analysis of Lung Function Test Parameters Using Mixed Model Repeated Measurement.

Variable Visit Treatment	N	LS Mean	Contrast: Inhaled treprostinil – Placebo Estimated Difference (95% CI)	P-value
FVC (mL)				
Week 8				
Inhaled treprostinil	142	5.49	28.47	0.35
Placebo	141	−22.98	(−30.81, 87.74)	
Week 16				
Inhaled treprostinil	130	9.77	44.40	0.21
Placebo	126	−34.63	(−25.25, 114.05)	
FVC (% predicted)				
Week 8				
Inhaled treprostinil	142	0.77	1.79	
Placebo	141	−1.02	(0.37, 3.21)	0.01
Week 16				
Inhaled treprostinil	130	1.07	1.80	0.03
Placebo	126	−0.72	(0.20, 3.39)	
FEV1 (mL)				
Week 8				
Inhaled treprostinil	142	−21.34	−8.95	0.72
Placebo	141	−12.39	(−57.16, 39.26)	
Week 16				
Inhaled treprostinil	130	−32.18	−2.56	0.93
Placebo	126	−29.62	(−57.67, 52.55)	
FEV1 (% predicted)				
Week 8				
Inhaled treprostinil	142	−0.18	0.57	0.43
Placebo	141	−0.75	(−0.83, 1.96)	
Week 16				
Inhaled treprostinil	130	−0.24	0.38	0.65
Placebo	126	−0.62	(−1.25, 2.01)	
TLC (mL)				
Week 8				
Inhaled treprostinil	135	−38.75	−16.23	0.80
Placebo	136	−22.51	(−141.9, 109.41)	
Week 16				
Inhaled treprostinil	127	45.43	17.37	0.85
Placebo	116	28.06	(−158.9, 193.61)	
TLC (% predicted)				
Week 8				
Inhaled treprostinil	135	−0.05	0.28	0.76
Placebo	136	−0.32	(−1.49, 2.05)	
Week 16				
Inhaled treprostinil	127	2.52	1.49	0.34
Placebo	116	1.03	(−1.57, 4.54)	
DLCO (mL/min/mmHg)				
Week 8				
Inhaled treprostini	136	−0.27	0.19	0.56
Placebo	136	−0.47	(−0.45, 0.84)	
Week 16				
Inhaled treprostinil	128	−0.61	0.02	0.96
Placebo	112	−0.63	(−0.73, 0.76)	
DLCO (% predicted)				
Week 8				
Inhaled treprostinil	136	−0.13	1.07	0.13
Placebo	136	−1.20	(−0.32, 2.47)	
Week 16				
Inhaled treprostinil	128	−1.14	0.60	0.44
Placebo	112	−1.74	(−0.93, 2.14)	

CI, confidence interval;
DLCO, diffusing capacity of the lungs for carbon monoxide;
FEV1, forced expiratory volume in 1 second;
FVC, forced vital capacity;
TLC, total lung capacity;;
LS Mean, least squares mean;
SE, standard error;
TLC, total lung capacity

LS Mean (SE), P-values, estimated difference (SE), and associated 95% CIs are from the mixed model repeated measurement with the change from Baseline in pulmonary function test parameter as the dependent variable; treatment, week, treatment by week interaction as the fixed effects; Baseline measurement as the covariate; and subject as the random effect. An unstructured variance/covariance structure shared across treatment groups was used to model the within-subject errors.

The confidence intervals and p-values have not been adjusted for multiplicity and cannot be used to infer definitive treatment effects.

TABLE 11

SpO_2 (%) Measured by Pulse Oximetry Results at Baseline and Week 16.

	Inhaled Treprostinil N = 163		Placebo N = 163		
Visit Statistic	Value	Change from Pre- walk	Value	Change from Pre- Walk	P-value*
Baseline Pre-walk SpO_2 (%)					
n	163		162		
Mean (SD)	95.3 (3.95)		94.5 (4.81)		
Median	96.0		96.0		
Min, Max	72, 100		68, 100		

TABLE 11-continued

SpO_2 (%) Measured by Pulse Oximetry Results at Baseline and Week 16.

Visit Statistic	Inhaled Treprostinil N = 163 Value	Inhaled Treprostinil N = 163 Change from Pre- walk	Placebo N = 163 Value	Placebo N = 163 Change from Pre- Walk	P-value*
Baseline During Walk SpO_2 (%)					
n	154	154	153	153	0.13
Mean (SD)	80.3 (8.22)	−15.0 (7.87)	78.5 (8.20)	−16.1 (7.76)	
Median	81.0	−14.0	78.0	−15.0	
Min, Max	53, 99	−41, 2	53, 98	−39, 4	
Baseline Post-walk SpO_2 (%)					
n	163	163	162	162	0.17
Mean (SD)	85.3 (7.31)	−9.9 (6.50)	83.7 (8.74)	−10.9 (8.06)	
Median	86.0	−10.0	83.5	−11.0	
Min, Max	59, 100	−26, 5	57, 99	−39, 7	
Week 16 Pre-walk SpO_2 (%)					
n	130		122		
Mean (SD)	94.5 (4.35)		94.5 (4.22)		
Median	95.0		95.0		
Min, Max	74, 100		78, 100		
Week 16 During Walk SpO_2 (%)					
n	123	123	114	114	0.27
Mean (SD)	76.8 (7.70)	−17.6 (7.01)	78.2 (9.28)	−16.6 (9.04)	
Median	77.0	−17.0	79.0	−16.0	
Min, Max	46, 99	−38, −1	28, 98	−61, −1	
Week 16 Post-walk SpO_2 (%)					
n	128	128	122	122	0.07
Mean (SD)	82.1 (9.24)	−12.4 (8.05)	83.7 (7.75)	−10.8 (7.09)	
Median	83.0	−13.0	84.0	−11.5	
Min, Max	51, 100	−29, 3	65, 100	−31, 6	

SD, standard deviation;

SpO_2, saturation of peripheral capillary oxygenation

*P-values are calculated from analysis of covariance with change from pre-walk as dependent variable, treatment as fixed effect, and baseline SpO_2 as covariate.

TABLE 12

Supplemental Oxygen Use (L/min) at Baseline and Week 16.

Visit Statistic	Inhaled Treprostinil N = 163 Value	Inhaled Treprostinil N = 163 Change from Baseline	Placebo N = 163 Value	Placebo N = 163 Change from Baseline	P-value*
Baseline Pre-walk (L/min)					
n	163		163		
Mean (SD)	2.7 (2.2)		2.4 (2.0)		
Median	3.0		2.0		
Min, Max	0, 10		0, 8		
Baseline During Walk (L/min)					
n	163		163		
Mean (SD)	4.9 (4.0)		4.5 (3.8)		
Median	4.0		4.0		
Min, Max	0, 25		0, 15		
Week 16 Pre-walk (L/min)					
n	131	131	129	129	0.18
Mean (SD)	3.0 (2.5)	0.4 (1.4)	2.9 (2.4)	0.6 (1.3)	
Median	3.0	0.0	3.0	0.0	
Min, Max	0, 10	−3, 6	0, 10	−3, 5	

TABLE 12-continued

Supplemental Oxygen Use (L/min) at Baseline and Week 16.

Visit Statistic	Inhaled Treprostinil N = 163 Value	Inhaled Treprostinil N = 163 Change from Baseline	Placebo N = 163 Value	Placebo N = 163 Change from Baseline	P-value*
Baseline During Walk (L/min)					
n	129	129	123	123	0.39
Mean (SD)	4.9 (4.0)	0.1 (0.8)	4.6 (3.7)	0.1 (0.3)	
Median	4.0	0.0	4.0	0.0	
Min, Max	0, 25	−2, 8	0, 15	0, 3	

SD, standard deviation

Subjects who did not use supplemental oxygen were coded as 0 in the summaries.

Subjects who received supplemental oxygen during the Baseline 6-minute walk test continued to receive the same flow rate at all subsequent 6-minute walk test assessments.

*P-values are calculated from analysis of covariance with change from baseline as dependent variable, treatment as fixed effect, and baseline oxygen use as covariate.

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Example 4. Aerosolized and Powder Inhaled Treprostinil

Randomized, 6-treatment, 6-period, 6-sequence, cross-over study (6×6 Williams design) in 36 healthy volunteers was performed to compare nebulized inhaled treprostinil administered by Tyvaso® nebulizer and Treprostinil inhalation powder (TreT) administered via a dry powder inhaler (published US Patent Application 20190321290). 4 subjects discontinued the study early (COVID-19, n=2; withdrawal by subject, n=1; non-compliance with study requirements, n=1).

Tyvaso Dose	TreT Dose
18 µg (3 nebulizer breaths)	16 µg cartridge
54 µg (9 nebulizer breaths)	48 µg cartridge
72 µg (12 nebulizer breaths)	64 µg cartridge

TABLE 14

Pharmacokinetic results for various doses for Tyvaso and TreT administered treprostinil. See also FIG. 9 and 10.

Comparison	Parameter	Geometric LSM (TreT) [CV %]	Geometric LSM (Tyvaso) [CV %]	Geometric LSM Ratio (%) [TreT/Tyvaso]	90% Confidence Interval
TreT 16 µg vs. Tyvaso 18 µg	AUC0-5	0.268 [24.1%]	0.233 [44.1%]	115	(104.59, 127.42)
	Cmax	0.377 [26.6%]	0.291 [59.8%]	130	(115.55, 145.95)
TreT 48 µg vs. Tyvaso 54 µg	AUC0-5	0.766 [21.8%]	0.757 [42.5%]	101	(91.63, 111.65)
	Cmax	1.07 [28.9%]	0.764 [53.4%]	139	(124.13, 156.73)
TreT 64 µg vs. Tyvaso 72 µg	AUC0-5	0.937 [23.8%]	1.02 [41.9%]	91.5	(83.16, 100.78)
	Cmax	1.27 [28.5%]	1.02 [54.7%]	124	(110.56, 139.61)

TABLE 15

Adverse events for various doses for Tyvaso and TreT administered treprostinil.

	TreT 16 μg N = 34 n (%)	Tyvaso 18 μg N = 34 n (%)	TreT 48 μg N = 34 n (%)	Tyvaso 54 μg N = 34 n (%)	TreT 64 μg N = 33 n (%)	Tyvaso 72 μg N = 35 n (%)
Adverse Events	16 (47.1)	13 (38.2)	23 (67.6)	21 (61.8)	22 (66.7)	25 (71.4)
Cough	15 (44.1)	11 (32.4)	20 (58.8)	18 (52.9)	21 (63.6)	24 (68.6)
Headache	2 (5.9)	3 (8.8)	4 (11.8)	7 (20.6)	6 (18.2)	6 (17.1)
Throat irritation	1 (2.9)	1 (2.9)	3 (8.8)	5 (14.7)	3 (9.1)	4 (11.4)
Dizziness	1 (2.9)	2 (5.9)	1 (2.9)	4 (11.8)	2 (6.1)	2 (5.7)
Nausea	0	0	0	2 (5.9)	2 (6.1)	1 (2.9)
Chest discomfort	1 (2.9)	0	3 (8.8)	2 (5.9)	0	2 (5.7)

Conclusions

AUC0-5 was generally comparable for each TreT and Tyvaso dose level. Cmax values for TreT were slightly higher than Tyvaso Cmax values across dose comparisons. AE profile consistent with known prostacyclin effects and previous studies of Tyvaso. Between-subject variability for both AUC0-5 and Cmax was approximately two-fold less for TreT compared to Tyvaso. AUC0-5 and Cmax for TreT and Tyvaso increased in an approximately dose-proportional manner. Median Tmax: ~10 minutes for TreT and ~10 to 15 minutes with Tyvaso.

Example 5. Aerosolized and Powder Inhaled Treprostinil. Safety Evaluation

Primary Objective

To evaluate the safety and tolerability of Treprostinil Inhalation Powder (TreT) administered by a dry powder inhaler, such as the one shown in FIG. **11**, in subjects with pulmonary arterial hypertension (PAH) currently treated with Tyvaso® (treprostinil inhalation solution administered via a nebulizer)

Secondary Objectives

To evaluate systemic exposure and pharmacokinetics (PK) of treprostinil in subjects with PAH when delivered as Tyvaso® and TreT. To evaluate 6-Minute Walk Distance (6MWD) at study entry and after 3 weeks of treatment with TreT. To evaluate subject satisfaction with and preference for TreT with the Preference Questionnaire for Inhaled Treprostinil Devices (PQ-ITD). To evaluate patient reported PAH symptoms and impact with the PAH-Symptoms and Impact Questionnaire (PAH-SYMPACT).

Eligibility Criteria

Diagnosis of WHO Group I PAH.

Subject must have started Tyvaso≥3 months prior to Baseline and on a stable regimen (no change in dose within 30 days of Baseline Visit) of Tyvaso (6 to 12 breaths QID).

Background therapy for PAH (eg, endothelin receptor antagonist or phosphodiesterase-5-inhibitor or both), on stable dose for a minimum of 30 days prior to Screening. Exclude other prostacyclin analogue or agonist (selexipag, epoprostenol, iloprost, or beraprost).

Excluding subjects with WHO Functional Class IV at Screening.

Subject is not able to perform inhalation maneuvers that meet inspiratory training criteria.

Exclude conditions which limits ambulation or ability to complete 6MWT (Baseline 6MWD>150 m).

Excluded initiation of pulmonary rehabilitation within 12 weeks prior to the Baseline Visit.

FIG. **12** shows a design of the study. Table 16 presents information relating Tret and Tyvaso doses.

TABLE 16

Tyvaso dose (QID)	TreT Dose (QID)	Device usage
6 to 7 breaths	32 μg	32 μg cartridge
8 to 10 breaths	48 μg	48 μg cartridge
11 to 12 breaths	64 μg	32 μg + 32 μg cartridges

TABLE 17

Baseline demographics	
Age (years)	
Median	57.0 (range: 23-82)
Sex, n (%)	
Female	43 (84.3)
Male	8 (15.7)
Current PAH Diagnosis, n (%)	
Idiopathic/familial	29 (56.9)
Associated with unrepaired/repaired congenital shunts	4 (7.8)
Associated with collagen vascular disease	14 (27.5)
Associated with HIV	1 (2.0)
Associated with appetite suppressant/ other drug or toxin use	3 (5.9)
WHO Functional Class at Screening, n (%)	
I	6 (11.8)
II	31 (60.8)
III	14 (27.5)

TABLE 12

Summary of Subject Accountability

	TreT Dose in Treatment Phase			
	32 mcg N = 2 n (%)	48 mcg N = 27 n (%)	64 mcg N = 22 n (%)	Overall N = 51 n (%)
Number of Subjects Enrolled	2	27	22	51
Received TreT	2 (100.0)	27 (100.0)	22 (100.0)	51 (100.0)
Enrolled in Optional Extension Phase	2 (100.0)	26 (96.3)	21 (95.5)	49 (96.1)
Subjects Who Discontinued Treatment Phase	0	1 (3.7)	1 (4.5)	2 (3.9)
Adverse Event	0	1 (3.7)	1 (4.5)	2 (3.9)
Subjects Who Discontinued OEP*	0	3 (11.1)	0	3 (5.9)
Adverse Event	0	2 (7.4)	0	2 (3.9)
Lost to Follow-up	0	1 (3.7)	0	1 (2.0)

TABLE 13

Summary of background PAH medication

	Overall N = 51; n (%)
ERA	43 (84.3%)
Ambrisentan	24 (47.1%)
Bosentan	2 (3.9%)
Macitentan	17 (33.3%)
PDE5-I	41 (80.4%)
Sildenafil	17 (33.3%)
Tadalafil	24 (47.1%)
sGC	7 (13.7%)
Riociguat	7 (13.7%)

Of the 51 subjects enrolled, assigned TreT doses for 3-week treatment period were 32 μg for 2 subjects; 48 μg for 27 subjects; 64 μg for 22 subjects. 49 subjects rolled into the Optional Extension Phase (OEP). FIG. **13** shows a number of subjects for various maintenance TreT doses in the OEP.

FIG. **14** shows a change in 6 minute walk distance (6MWD) with respect to a baseline 6MWD as a function of duration of TreT treatment. The change from Baseline in 6MWD for TreT overall demonstrated a significant improvement (11.5 m increase; p=0.0217) at Week 3. The improvements in 6MWD for TreT overall were sustained in the Optional Extension Phase.

Patient Reported Outcome Measures

The PQ-ITD is a patient-reported outcome questionnaire to evaluate subject satisfaction with and preference for inhaled treprostinil devices. The PQ-ITD was given at Baseline to evaluate the Tyvaso Inhalation System and at Week 3 to evaluate the TreT Inhaler.

The distribution of responses to each question on the PQ-ITD was significantly improved (p≤0.0003) between Baseline (Tyvaso nebulizer) and Week 3 (TreT inhaler). Overall satisfaction with the TreT inhaler was significantly improved at Week 3 (95.7%, p<0.0001) compared to satisfaction with the Tyvaso nebulizer at Baseline, FIG. **14**.

PAH SYMPACT

The PAH-SYMPACT is a well validated patient-reported outcome questionnaire given to assess PAH symptoms and effects. The PAH-SYMPACT contains four domains (Cardiopulmonary Symptoms, Cardiovascular Symptoms, Physical Impacts, Cognitive/Emotional Impacts) and was given at Baseline, Week 3, and Week 11.

Analysis of patient-reported PAH SYMPACT data revealed a trend of improvement at both Week 3 and Week 11 for subjects receiving TreT.

Mean change from Baseline was lower for all domain scores of the PAH-SYMPACT at both weeks (range: −0.05 to −0.22), with significant improvements for physical impacts (range: −1.1 to 1.0; p=0.0438) and cognitive/emotional impacts (range: −1.3 to 0.5; p=0.0048) at Week 3.

TABLE 18

Overall Safety

	TreT Dose in Treatment Phase			
Treatment Phase	32 mcg N = 2 n (%)	48 mcg N = 27 n (%)	64 mcg N = 22 n (%)	Overall N = 51 n (%)
Total number of AEs	0	37	22	59
Total number of SAEs	0	1	1	2
AEs leading to withdrawal of study drug	0	1	1	2
Optional Extension Phase	0			
Total number of AEs	2	51	29	82
Total number of SAEs	0	10	4	14
AEs leading to withdrawal of study drug	0	3	0	3

TABLE 19

Most frequent adverse events during the treatment phase

	Treatment Phase Dose				TRIUMPH	
Preferred Term	32 mcg N = 2 n (%)	48 mcg N = 27 n (%)	64 mcg N = 22 n (%)	Overall N = 51 n (%)	Tyvaso n (%)	Placebo n (%)
Cough	0	9 (33.3)	4 (18.2)	13 (25.5)	62 (54)	35 (29)
Headache	0	4 (14.8)	4 (18.2)	8 (15.7)	47 (41)	27 (23)

TABLE 19-continued

Most frequent adverse events during the treatment phase

	Treatment Phase Dose				TRIUMPH	
	32 mcg	48 mcg	64 mcg	Overall		
Preferred Term	N = 2 n (%)	N = 27 n (%)	N = 22 n (%)	N = 51 n (%)	Tyvaso n (%)	Placebo n (%)
Dyspnoea	0	2 (7.4)	1 (4.5)	3 (5.9)	6 (5)	6 (5)
Flushing	0	1 (3.7)	1 (4.5)	2 (3.9)	17 (15)	1 (<1)
Nausea	0	2 (7.4)	0	2 (3.9)	22 (19)	13 (11)
Throat irritation	0	1 (3.7)	1 (4.5)	2 (3.9)	29 (25)*	17 (14)*

*TRIUMPH groups together Throat Irritation and Pharyngolaryngeal Pain.

TABLE 20

Most frequent adverse events during the treatment phase during the optional extension phase

	TreT Dose in Treatment Phase			
Preferred Term	32 mcg N = 2 n (%)	48 mcg N = 26 n (%)	64 mcg N = 21 n (%)	Overall N = 49 n (%)
Cough	0	3 (11.5)	2 (9.5)	5 (10.2)
Dyspnoea	1 (50.0)	2 (7.7)	2 (9.5)	5 (10.2)
Headache	0	2 (7.7)	2 (9.5)	4 (8.2)
Diarrhoea	0	1 (3.8)	2 (9.5)	3 (6.1)
Pneumonia	0	2 (7.7)	1 (4.8)	3 (6.1)
Arthralgia	0	2 (7.7)	1 (4.8)	3 (6.1)
Dizziness	0	2 (7.7)	1 (4.8)	3 (6.1)

Conclusions

Transition from Tyvaso to TreT was safe and well tolerated in this study. Most adverse effects (AEs) were mild to moderate in severity and occurred at severities and frequencies consistent with those seen in other inhaled treprostinil studies in patients with PAH.

Following 3 weeks of TreT administration, subjects switching from Tyvaso to TreT demonstrated:

Significant improvements in 6MWD (8.0 m increase; p=0.0217) at Week 3. As of 23 Dec. 2020 (data cut-off date), improvements in 6MWD for TreT overall were sustained in the OEP Significant satisfaction with and preference for the use of the TreT inhaler (PQ-ITD) Significant improvement in PAH impact scores, and a trend of improvement in PAH symptom scores (PAH SYMPACT).

Additional Embodiments

1. A method of treating interstitial lung disease (ILD) or pulmonary fibrosis in a subject in need, comprising administering to the subject a therapeutically effective amount of treprostinil, a prodrug, salt, or ester thereof.

2. A method of reducing pulmonary function decline in a subject with interstitial lung disease (ILD) or pulmonary fibrosis, comprising administering to the subject treprostinil, a prodrug, salt, or ester thereof.

3. A method of increasing forced vital capacity (FVC) in a subject suffering from ILD or pulmonary fibrosis, comprising administering to the subject treprostinil, a prodrug, salt, or ester thereof.

4. The method of any one of embodiments 1-3, wherein the ILD comprises one or more of idiopathic pulmonary fibrosis (IPF), desquamative interstitial pneumonia (DIP), acute interstitial pneumonia (AIP), nonspecific interstitial pneumonia (NSIP), respiratory bronchiolitis-associated interstitial lung disease (RB-ILD), cryptogenic organizing pneumonia (COP), lymphoid interstitial pneumonia (LIP), sarcoidosis, rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, polymyositis, dermatomyositis, antisynthetase syndrome, silicosis, asbestosis, occupational lung disease, chronic hypersensitivity pneumonitis, idiopathic interstitial pneumonia (IIP), an autoimmune ILD, lymphangioleiomyomatosis (LAM), Langerhan's cell histiocytosis (LCH), drug associated ILD, vasculitis, granulomatosis, and berylliosis.

5. The method of embodiment 4, wherein the ILD comprises IPF.

6. The method of any one of embodiments 1-5, wherein the ILD comprises systemic sclerosis-associated interstitial lung disease (SSc-ILD).

7. The method of any one of embodiments 1-6, wherein the ILD was induced from antibiotics, chemotherapy, antiarrhythmic agents, coronavirus disease 2019, atypical pneumonia, pneumocystis pneumonia, tuberculosis (TB), *Chlamydia trachomatis*, respiratory syncytial virus, or lymphangitic carcinomatosis.

8. The method of any one of embodiments 1-7, wherein the subject has one or more of surfactant-protein-B deficiency, surfactant-protein-C deficiency, ABCA3-deficiency, brain lung thyroid syndrome, congenital pulmonary alveolar proteinosis, alveolar capillary dysplasia, mutations in telomerase reverse transcriptase, mutations in telomerase RNA component, mutations in the regulator of telomere elongation helicase 1, and mutations in poly(A)-specific ribonuclease.

9. The method of any one of embodiments 1-8, wherein the subject has one or more symptoms of shortness of breath, fatigue, weight loss, dry cough, chest pain, and lung hemorrhage.

10. The method of embodiment 9, wherein after administration the symptom is improved by about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, or about 100%, as measured by a medically-recognized technique.

11. The method of embodiment 10, wherein the medically-recognized technique comprises one or more of Modified Medical Research Council (MMRC) Dyspnoea Scale, Modified Borg Dyspnoea Scale (0-10), Chalder Fatigue Scale, weight measurement scale, visual analogue scale (VAS) for cough, King's Brief Interstitial Lung Disease Questionnaire, Leicester Cough Questionnaire (LCQ), computed tomography (CT) scan, X-ray, multiple magnetic

resonance imaging (MRI), pulmonary function testing (PFT), spirometry, lung volumes, maximal respiratory pressure, diffusing capacity, oxygen desaturation, and arterial blood gas evaluation.

12. The method of any one of embodiments 1-11, wherein treprostinil, a prodrug, salt, or ester thereof is administered in a pharmaceutical composition comprising treprostinil, a prodrug, salt, or ester thereof and a pharmaceutically acceptable carrier or excipient.

13. The method of claim any one of embodiments 1-12, wherein the administration comprises at least one of oral, inhalation, subcutaneous, nasal, intravenous, intramuscular, sublingual, buccal, rectal, vaginal, and transdermal administration.

14. The method of any one of embodiments 1-13, wherein the administration comprises inhalation.

15. The method of any one of embodiments 1-14, wherein a single inhalation administration event comprises from 1 to 20 breaths.

16. The method of any one of embodiments 1-15, comprising administration of at least one additional active agent to treat the IRD.

17. The method of embodiment 16, wherein the at least one additional active agent comprises a corticosteroid, mycophenolic acid, mycophenolate mofetil, azathioprine, cyclophosphamide, rituximab, pirfenidone, or nintedanib.

18. The method of embodiment 16 or 17, wherein the at least one additional active agent and treprostinil, a prodrug, salt, or ester thereof, are administered via a method selected from the group consisting of

(a) concomitantly;

(b) as an admixture;

(c) separately and simultaneously or concurrently; and

(d) separately and sequentially.

19. The method of any one of embodiments 1-18, wherein administration is once, twice, thrice, four times, five times, or six times per day.

20. The method of any one of embodiments 1-19, wherein administration is for a period selected from the group consisting of about 1 day, about 1 day to about 3 days, about 3 days to about 6 days, about 6 days to about 9 days, about 9 days to about 12 days, about 12 days to about 15 days, about 15 days to about 18 days, about 18 days to about 21 days, about 21 days to about 24 days, about 24 days to about 27 days, about 27 days to about 30 days, or about greater than 30 days.

21. The method of any one of embodiments 1-20, wherein the subject is a human.

22. The method of any one of embodiments 1-21, wherein the method results in an increased FVC compared to the FVC at the start of or prior to the start of administration.

23. The method of embodiment 22, wherein the administration results in an increased FVC at sixteen weeks after the start of administration compared to the FVC at the start of or prior to the start of administration.

24. The method of any one of embodiments 22-23, wherein the increase in FVC is at least 20%.

25. The method of embodiment 24, wherein the increase is FVC is at least 75%.

Although the foregoing refers to particular preferred embodiments, it will be understood that the present invention is not so limited. It will occur to those of ordinary skill in the art that various modifications may be made to the disclosed embodiments and that such modifications are intended to be within the scope of the present invention.

All of the publications, patent applications and patents cited in this specification are incorporated herein by reference in their entirety.

What is claimed is:

1. A method of improving exercise capacity in a patient having pulmonary hypertension associated with interstitial lung disease, comprising administering by inhalation to the patient having pulmonary hypertension associated with interstitial lung disease an effective amount of at least 15 micrograms up to a maximum tolerated dose of treprostinil or a pharmaceutically acceptable salt thereof in a single administration event that comprises at least 6 micrograms per breath.

2. The method of claim **1**, wherein said administering provides a statistically significant increase of a 6 minutes walk distance in the patient after 8 weeks, 12 weeks, or 16 weeks of the administering.

3. The method of claim **1**, wherein said administering increases a 6 minutes walk distance of the patient by at least 10 m after 8 weeks, 12 weeks, or 16 weeks of the administering.

4. The method of claim **1**, wherein said administering provides a statistically significant reduction of a plasma concentration of NT-proBNP in the patient after 8 weeks, 12 weeks, or 16 weeks of the administering.

5. The method of claim **1**, wherein said administering reduces a plasma concentration of NT-proBNP in the patient by at least 200 pg/ml after 8 weeks, 12 weeks, or 16 weeks of the administering.

6. The method of claim **1**, wherein said administering provides a statistically significant reduction of at least one exacerbations of the interstitial lung disease.

7. The method of claim **1**, wherein said administering provides a statistically significant reduction of clinical worsening events due to the interstitial lung disease.

8. The method of claim **7**, wherein the clinical worsening events comprise at least one of hospitalization for cardiopulmonary indication and a decrease in a 6-minute walk distance by more than 15% compared a baseline 6-minute walk distance prior to the administering.

9. The method of claim **1**, wherein said administering provides a statistically significant improves of forced vital capacity (FVC) in the patient after 8 weeks, 12, weeks or 16 weeks of the administering.

10. The method of claim **9**, wherein said administering improves the forced vital capacity (FVC) in the patient by at least 20 ml after 8 weeks, 12 weeks, or 16 weeks of the administering.

11. The method of claim **1**, wherein said administering is performed by a pulsed inhalation device.

12. The method of claim **11**, wherein the pulsed inhalation device contains an inhalation solution comprising treprostinil or a pharmaceutically acceptable salt thereof.

13. The method of claim **11**, wherein the pulsed inhalation device is a nebulizer.

14. The method of claim **11**, wherein the pulsed inhalation device is a dry powder inhaler comprising a dry powder comprising treprostinil or a pharmaceutically acceptable salt thereof.

15. The method of claim **1**, wherein the effective amount of treprostinil or a pharmaceutically acceptable salt administered to the patient in a single inhalation administration event is from 15 μg to 100 μg.

16. The method of claim **15**, wherein the single inhalation administration event does not exceed 15 breaths by the patient.

17. The method of claim **1**, wherein said administering increases a 6 minutes walk distance of the patient by at least 10 m after 8 weeks of the administering.

18. The method of claim **1**, wherein said administering increases a 6 minutes walk distance of the patient by at least 15 m after 12 weeks of the administering.

19. The method of claim **1**, wherein said administering increases a 6 minutes walk distance of the patient by at least 15 m after 16 weeks of the administering.

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